

CHALLENGES FACING THE SUCCESSFUL INTRODUCTION OF PLANT-DERIVED VACCINES AS AN ALTERNATIVE OR COMPLEMENT TO CONVENTIONAL VACCINES

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By

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ABSTRACT

Vaccines are considered to be one of the most successful and cost-effective weapons against infectious diseases. Currently, licensed vaccines produced in mammalian cell lines, yeast, and the common enteric bacterium *Escherichia coli* have their associated technical problems. A decade-old R&D project of developing vaccines in plants has yielded promising results, addressing the technical issues to a great extent with the added benefit of faster and cheaper production. Plant-derived vaccines (PDVs) are therefore poised to play an important role in complementing conventional seasonal and pandemic vaccine supply.

This study of the introduction of the concept of PDV and its adoption into the society is a prototypical third-generation plant biotechnology with backgrounds encompassing agricultural practice, public health, and medical biotechnology research. The primary objective of this thesis is to understand the public good and private interests in the introduction and adoption of PDVs. Critical analyses of PDV innovation from biotechnology business case studies within the frameworks of existing socio-economic, organizational theories, and emerging non-socio-economic networked knowledge has been undertaken in this thesis.

Among other things, this thesis found that (i) new research-intensive biotechnology small- and medium-sized enterprises (SMEs, with 5–499 employees) can reduce their transaction costs by working in research networks (primarily public–private partnerships); and (ii) by forming strategic partnerships with companies that have established manufacturing and distribution networks, these SMEs increase their chances of accessing capital and other resources. This significantly increases the probability of commercial success by SMEs in the highly competitive environment of global vaccine business.

It is anticipated that this understanding will help improve the facilitation of R&D, and the regulation and production of PDVs in Canada and the USA. Research findings address the policy implications for governments, industry, and the non-governmental organization sector. The knowledge generated from this thesis will contribute to the optimization of local and international research, intellectual property protection, licensing, manufacturing, and distribution of PDVs or other vaccine entities/companies. Ultimately, it is hoped that this thesis knowledge will lead to more rapid and widespread adoption of new vaccines such as PDVs in developing countries, where its potential benefits of scale, lower cost, and shorter production time would be best realized.

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DEDICATION

I would like to dedicate my research thesis to my loving parents: mom, Bharati Das, and dad, Pranab Das. My wonderful folks have always taught me life skills and positively supported my endeavours. Love you always.

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LIST OF ABBREVIATIONS

AAFC - Agriculture and Agri-Food Canada
ASU - Arizona State University
CAMR - Canada's Access to Medicines Regime
CECR - Centres of Excellence for Commercialization and Research
CEO - Chief Executive Officer
CFIA - Canadian Food Inspection Agency
CFS - Center for Food Safety
cGMP - current Good Manufacturing Practices
CHVI - Canadian HIV Vaccine Initiative
CIHR - Canadian Institutes of Health Research
DARPA – US Defense Advanced Research Projects Agency
DND Canada - Canadian Department of National Defence
DRDC - Defence Research and Development Canada
EFSA - European Food Safety Authority
EIS - Environmental impact statement
EMA - European Medicines Agency
GAVI - Global Alliance for Vaccines and Immunisation Alliance
GE - Genetically engineered
GM - Genetically modified
GSK - GlaxoSmithKline
HIV/AIDS - Human immunodeficiency Virus/Acquired Immunodeficiency Syndrome
IND - Investigational New Drug application
IP - Intellectual property
LMI - Low- and middle-income countries
MSF - Médecins Sans Frontières
NCE - Networks of Centres of Excellence
NRC Canada - National Research Council of Canada
NSERC - Natural Sciences and Engineering Research Council
PDV – Plant-derived vaccine
PHAC - Public Health Agency of Canada
PMI - Phillip Morris International
PPP - Public–private partnership
PREVENT - Pan-Provincial Vaccine Enterprise
SARS - Severe Acute Respiratory Syndrome
SME - Small- and medium-sized enterprises
SSHRC - Social Sciences and Humanities Research Council of Canada
TRIPS Agreement - Agreement on Trade-related Aspects of Intellectual Property Rights
UBC - University of British Columbia
UCS - Union of Concerned Scientists
USDA - US Department of Agriculture
FDA - US Food and Drug Administration
VIC - BIOTEC Canada Vaccine Industry Committee
VIDO - Vaccines and Infectious Disease Organization

VLP - Virus-like particles
WTO - World Trade Organization

1. INTRODUCTION

Chapter 1 provides an overview of vaccines, an introduction to plant-derived vaccines (PDVs), and a description of the structure and objectives of the thesis.

1.1 Issue: Vaccines and Biotechnology

Antibiotics as microbial intervention tools have been used extensively since World War II; but as the concerns of multi-spectrum antibiotic resistance rises both in human clinical practice and agriculture [1, 2], alternative tools are being pursued. Vaccines are considered to be one of the most successful and cost-effective public health tools against infectious diseases to this date [3].

Vaccines in Western society have come a long way from their humble beginnings, starting with Edward Jenner's crude smallpox inoculation initiatives in late-18th century England, through to Louis Pasteur's development of the first vaccine to protect humans against rabies in 1885 [3], to the contemporary mass production of clinical grade vaccines using modern biotechnology to immunize populations worldwide. Traditionally vaccines (i.e., prophylactic vaccines) have been used to produce protective immunity prior to exposure to infection causing microorganism.

However, vaccines (or immunotherapeutics) that can stimulate immunity in an already infected individual against some retroviral infections (particularly HIV) are also gaining importance [4]. All prophylactic vaccines used for routine immunization are effective in preventing diseases [3].

1.1.1 The Science Behind Vaccines

The success of current vaccines against most viral and bacterial infections is due to the primary protection that is thought to be mediated by a long-lived humoral immune response through the production of antibodies (triggered by detection of an antigen by the immune system) [5]. There are no uniformly effective vaccines against many infections that result in a substantial number of deaths worldwide, including tuberculosis, malaria and HIV. Although humoral immunity could be important in preventing HIV infection and certain stages of malaria infection, it is the cellular immune response that is central to the mediation of protection in all of these diseases. The acquired cellular immune response is composed of CD4⁺ and CD8⁺ T cells that recognize antigens [4, 5].

Ulmer et al. [6] outline the three key components of an effective vaccine: first, an antigen against which adaptive immune responses are generated; second, an immune stimulus or adjuvant to signal the innate immune system to potentiate the antigen-specific response; and third, a delivery system to ensure that the antigen and adjuvant are delivered together at the right time and location. Fig.1.1 illustrates these key components of an effective vaccine assembly.

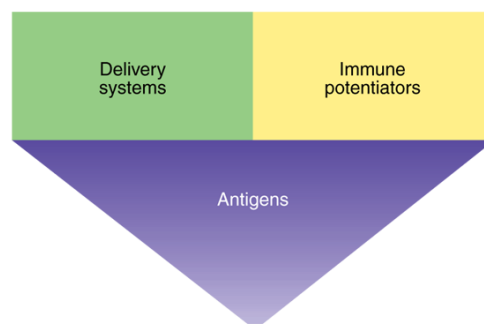


Figure 1.1: Main Elements of an Effective Vaccine (From [6]).

1.1.2 Types of Vaccines

Vaccines can be classified based on their constitution [3, 6, 7]: killed, intact virus (e.g., injected polio vaccine); live, weakened virus (e.g., oral polio vaccine); killed, intact bacteria (e.g., vaccine for typhoid); live, attenuated (or weakened) viruses (e.g., vaccines against measles and the other standard “childhood” diseases — mumps, chickenpox, and rubella); mixture of inactivated toxins (e.g., vaccines for diphtheria and tetanus); killed, “disrupted” viruses (e.g., influenza vaccines); and a mixture of highly purified complex polysaccharides taken from bacterial coats or capsules (e.g., vaccines against *Haemophilus influenzae* type b (Hib), pneumococcal, and meningococcal disease).

In the subunit vaccine approach, whole organisms are replaced by use of purified antigens (e.g., *Bordetella pertussis* antigens in the acellular DPT vaccine) [8]. In recombinant vaccines, genes for desired antigens are inserted into a vector (usually a virus) with very low virulence; the vector expressing the antigen may be used as the vaccine, or the antigen may be purified and injected as a subunit vaccine [8]. The first recombinant subunit vaccine licensed for use in humans was the Hepatitis B Virus (HBV) vaccine. In the HBV vaccine, the Hepatitis B surface antigen is produced from a gene transfected into yeast cells and purified for injection as a subunit vaccine. Advantages of recombinant vaccines are that the vector can be chosen to be safe, and be easy to grow and store, thereby also reducing production costs. Further, in these vaccines, antigen selection can be done in a way that the antigens that do not elicit protective immunity or that elicit damaging responses can be eliminated. Disadvantages of recombinant vaccines are their cost of development, which includes location of genes for the desired antigens, cloning, and efficient expression in the new vector. It has been argued that subunit recombinant vaccines are

unable to evoke a strong enough immune response on their own, so manufacturers add immune enhancers called adjuvants [7, 9].

Table 1.1 shows the major types of vaccines, and the related approaches are illustrated in Fig.

1.2.

Table 1.1: Major Types of Vaccines (From [6]).

| Vaccine Type | Selected Disease Targets | Vaccine Preparation |
|----------------------------|-----------------------------|---|
| Live attenuated | Smallpox | Crude preparation of cowpox infected calf skin |
| | Tuberculosis | <i>Mycobacterium bovis</i> BCG grown in media |
| | Yellow fever | Purified, attenuated virus grown in eggs |
| | Polio | Purified, attenuated virus grown in tissue culture cells |
| | Chickenpox | Purified, attenuated virus grown in tissue culture cells |
| | Rotavirus | Purified, attenuated virus grown in tissue culture cells |
| | Influenza | Purified, attenuated virus grown in eggs |
| Killed | Typhoid fever | Inactivated <i>Salmonella typhi</i> grown in media |
| | Plague | Inactivated <i>Yersinia pestis</i> grown in media |
| | Whooping cough | Inactivated whole-cell <i>Bordetella pertussis</i> grown in media |
| | Influenza | Inactivated virus grown in eggs |
| | Polio | Inactivated virus grown in tissue culture cells |
| | Hepatitis A | Inactivated virus grown in tissue culture cells |
| | | |
| Purified subunit | Diphtheria | Inactivated toxin from <i>Corynebacterium diphtheriae</i> grown in media |
| | Tetanus | Inactivated toxin from <i>Clostridium tetani</i> grown in media |
| | Pneumococcus | Polysaccharides from 23 <i>Streptococcus pneumoniae</i> strains grown in media |
| | Meningococcus | Polysaccharides from four <i>Neisseria meningitidis</i> strains grown in media |
| | Hib | Polysaccharides from <i>H. influenzae</i> chemically conjugated to carrier protein |
| | Pertussis | Acellular extract of <i>B. pertussis</i> grown in media |
| | Anthrax | Culture supernatant of <i>Bacillus anthracis</i> grown in media |
| Recombinant subunit | Hepatitis B | Purified, recombinant HBsAg Virus like particles (VLP) produced in tissue culture cells |
| | <i>Borrelia burgdorferi</i> | Purified, recombinant OspA protein produced in tissue culture cells (discontinued since 2002) |

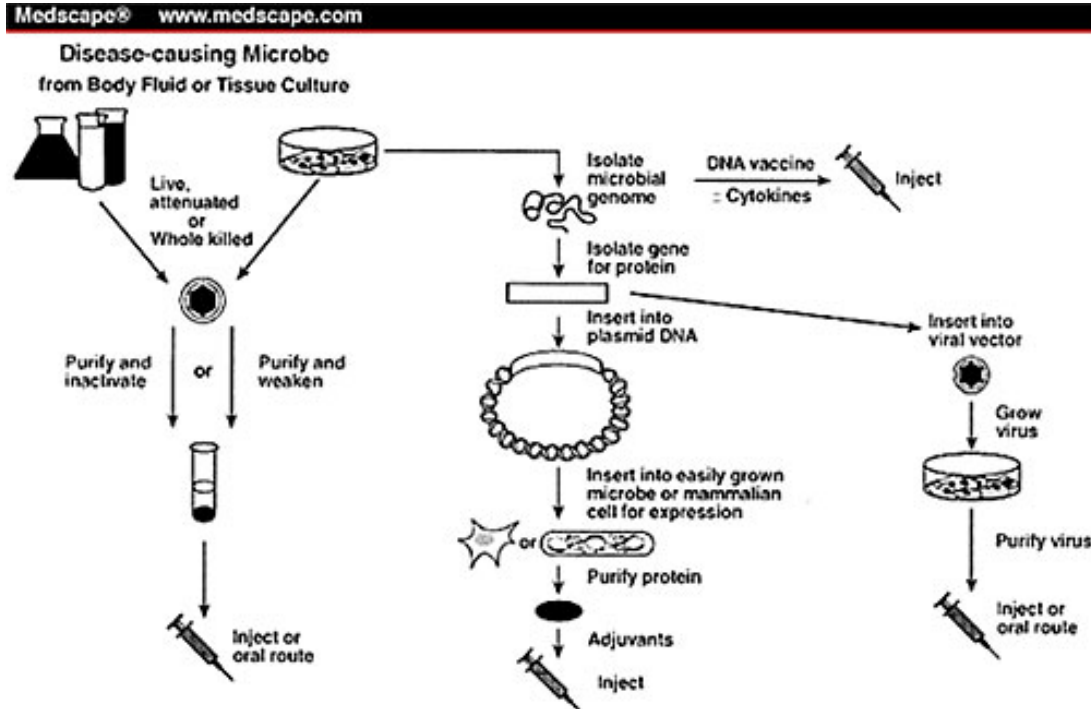


Figure 1.2: Vaccine Development Strategies (From [10]).

Various types of approaches to develop vaccines against retroviral infections (e.g., HIV) have been reviewed in prior literature [4]. They can be classified as: (i) passive immunotherapy that involves passage of antibodies (antiviral sera and monoclonal antibodies) from an individual who has encountered an antigen to an unaffected individual; (ii) vaccines that induce humoral immunity (inactivated virus, subunit and peptide vaccines); (iii) vaccines that induce cell mediated immunity as well as humoral immunity (attenuated viruses, vaccinia/avipox based vaccines, retroviral vectors, and direct DNA injection); and (iv) vaccines based on bacteria (*Bacillus Calmette-Guérin BCG*, *Salmonella*, etc.).

Virus-like particles (VLPs) are formed by self-assembly of viral capsid proteins upon expression in cell culture systems [6]. VLP-based vaccines have several potential advantages. First, they are particulate, meaning they contain many copies of antigen in a repeating array and present conformational antibody epitopes, thereby mimicking viral surface structure. These properties render VLPs very efficient for induction of both humoral and cell-mediated immunity. Second, they do not package viral nucleic acids and are thus non-replicating and very safe. Third, they have been shown to be effective when administered mucosally, including orally. Finally, VLPs can be produced in a variety of expression systems, such as mammalian, insect, yeast, bacteria, and plant cells, which provides flexibility in tailoring manufacturing conditions to the specific needs of the product, such as the requirement for mammalian post-translational processing.

New vaccine technologies have been covered in prior literature. Gene-based vaccines consisting of plasmid DNA or recombinant viral vectors efficiently induce cellular immunity [6], and would potentially be efficient against tuberculosis, malaria, and HIV (as discussed above in section 1.1.1).

In addition to the above, novel adjuvants and delivery systems are also being developed to complement the emerging vaccine technologies.

1.1.3 A Comeback

Vaccines used to be considered as low-profit, high-risk biological products. In large multinational pharmaceutical companies, commitment to vaccine manufacturing competed for R&D resources against other products with high profit potential such as those against heart

disease and cancer [9, 11]. For the past 15 years, vaccines have been fast losing the above connotation as private companies are now turning their attention to strengthen their vaccine candidate pipelines. The driving forces behind the above development are science, economics and health politics. Some examples of the driving forces include delivery of multibillion dollar products such as Wyeth's Prevnar (the world's first pneumococcal vaccine for children, acquired by Pfizer) and Merck's Gardasil (against human papillomavirus/HPV). Also, in the early- and mid-2000s, pandemic influenza preparedness plans, increased public and private investment in vaccines, big pharmaceutical companies losing profits to competition from generics, drying product pipelines, and increased regulation and associated costs all interacted to change the vaccine landscape [7, 9].

The global vaccine market, valued at approximately US\$16.3 billion in 2007, is projected to increase at an annual rate of roughly 13-14% over the next several years—more than twice as rapidly as for traditional pharmaceuticals—and is expected to exceed US\$30 billion by 2013 [47]. Based on aggregate data provided in 2008 by members of the BIOTEC Canada Vaccine Industry Committee (VIC), annual vaccine sales in Canada are currently estimated at approximately \$450 million (public spending about \$250 million, private about \$200 million) [47].

1.2 Problem: Plant-Derived Vaccines

The research concept of plant-derived vaccines (PDVs) was proven, and promising products created were presented by the author of this thesis in a 2008 publication [12], emphasizing the advantages of the plant platform over conventional vaccines, and the challenges facing the

introduction of PDVs to address current vaccine manufacturing shortages. It was concluded in the publication [12] that the remaining scientific and technological challenges being surmountable, the successful strategy for introduction and adoption of PDVs had to rely on continued public support as an investment in public good.

Currently, vaccines have been developed using mammalian cell lines, yeast, and the common enteric bacterium *Escherichia coli* (*E. coli*), but these systems have technical problems that include scalability, contamination, and multiple co- or post-translational modifications (glycosylation). In addition to being able to avoid all the above problems to some extent, PDVs can be produced faster and cheaper [13]. PDVs are proposed to play an important role in complementing conventional vaccine supply. The section below focuses attention on the potential role of PDVs in pandemic vaccine supply. Figure 1.3 illustrates the probable effect of plant production of vaccine antigen compared to conventional production on the lower pricing of a vaccine. It was shown that using plants could yield 68% savings in total production costs compared to using conventional methods. Table 1.2 shows significant savings that can be made by producing PDVs compared to conventional vaccines against HBV in three different regions and two different dosage forms, justifying the establishment of a comprehensive program to bring one or more products to the market soon.

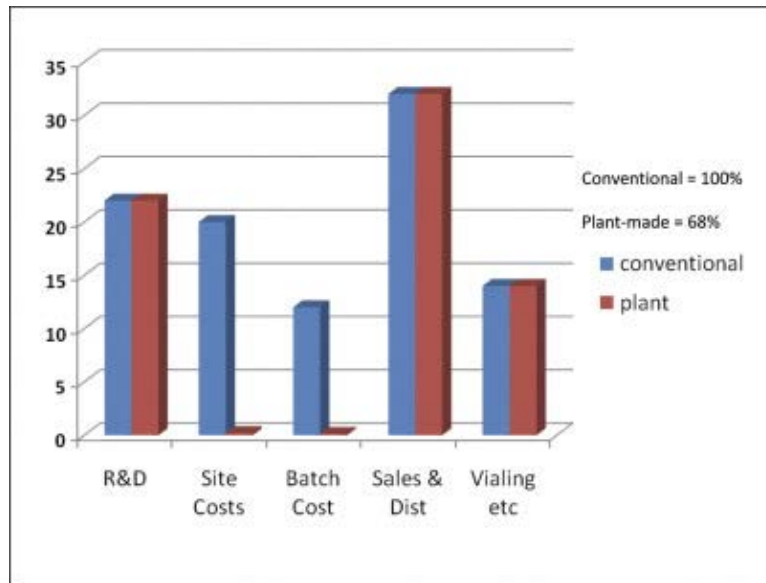


Figure 1.3: Comparative Costs of PDVs and Conventional Vaccines (From [14]). Bars represent the percentage contribution of the different components shown to the final wholesale price of a vaccine. Each cost component, e.g., R&D, consists of two bars: blue (left) represents conventional platform and red (right), plant platforms.

Table 1.2: Comparison of Production and Effective Cost with PDVs (Adapted from [15]).

| Countries | Korea or India | United States | | Korea | | India | |
|-----------------------|-----------------------------|--------------------|----------------|--------------------|----------------|--------------------|----------------|
| Production System | Yeast | Plant-derived | | Plant-derived | | Plant-derived | |
| Packaging/dosage sold | Yeast-derived 10-dose vials | single-dose packet | 10-dose packet | single-dose packet | 10-dose packet | single-dose packet | 10-dose packet |
| Cost (US\$) | 0.27 | 0.15 | 0.06 | 0.09 | 0.04 | 0.075 | 0.03 |
| Effective Cost | 0.42 | 0.16 | 0.08 | 0.10 | 0.05 | 0.08 | 0.04 |
| % Savings* | 0 | 62 | 81 | 76 | 88 | 81 | 90 |

* For plant-derived vaccine against yeast-derived for effective cost. Effective cost is cost per dose to deliver in a developing country immunization program.

1.2.1 Challenges Facing PDVs

Previous literature has covered this issue [16]. Ongoing efforts to produce alternatives to established vaccines—such as those to Hepatitis B Virus (HBV), HPV, and rotaviruses—face competition from the enormous and well-established conventional capacity for production of generics, as in the case of HBV, which is cheap enough to be included in the universal infant vaccination bundle recommended by the World Health Organization (WHO) Expanded Programme on Immunization. The other challenge is the huge capital required in development and production plants for the new HPV and rotavirus vaccines, which discourages big pharmaceutical companies from diversifying their means of production. It is thus argued that PDV technologies capitalize on their competitive advantages—the huge range in scalability and speed of response—ideally suited for niche “orphan vaccines” (e.g., Lassa fever and the South American haemorrhagic fever viruses), or emerging disease vaccines with pandemic potential (see section on Pandemic Preparedness below), or even bio-terror threats, where other means of production are simply too slow to respond [16]. The lack of momentum in pull forces from governments and markets for PDVs has been reviewed by researchers [14] and ways to potentially address them are discussed in Chapter 5 (section 5.1.1).

Currently, inactivated seasonal influenza vaccines are produced in embryonated eggs. The egg-based systems suffer from limited capacity, poor flexibility, and restricted responsiveness, decreasing the effectiveness of this system in a pandemic [17]; in response to the associated problems, alternative systems to complement supply have been proposed. The egg-based seasonal influenza vaccines are produced twice yearly and take six months after the identification of influenza strains by WHO global influenza surveillance system [18]. Other

platforms require a shorter time to produce vaccines, e.g., plant-based (14 days) and insect-cell culture and recombinant baculovirus cultures (11 weeks) [9, 19]. Considering competitive advantages in terms of higher speed and lower cost that are of great importance in pandemics, PDVs are clearly positioned to complement, if not substitute, the conventional pandemic (and seasonal) influenza vaccine supply. There is ample evidence from research groups worldwide that suggest plants may be a uniquely viable vehicle for rapid response or even conventional vaccine production for the prevention of influenza [16].

1.2.2 Social Issues

The potential advantages of PDVs, namely, that they are safe, cheap, and fast to produce, have been already established. PDVs fit within the scientific areas of genetically modified (GM) crops and vaccines. PDVs thus inherit some controversies of both GM crops and vaccines. Past experiences of social dynamics with GM crops suggest that society reacts to controversies. The controversies in this case are inherited from GM crops: the perception of the possibilities of contamination of the food supply (supported by scientific evidence, see section 1.2.3), the potential for the development of immunological tolerance to orally dosed or edible vaccines, and the potential for regulatory and production problems [14]. While perception of the possibilities of contamination of the food supply is within the realm of social sciences understanding, the rest are more technical and political. Potential regulatory problems and perception of the possibility of contamination of the food supply would involve the public and voluntary sectors (areas A & E respectively in Figure 1.4 below), which is discussed further down in this section. Anticipating and addressing social challenges to the introduction of this new technology is important for fully

realizing the potential benefits in developing and underdeveloped countries where the vaccines are much needed [21].

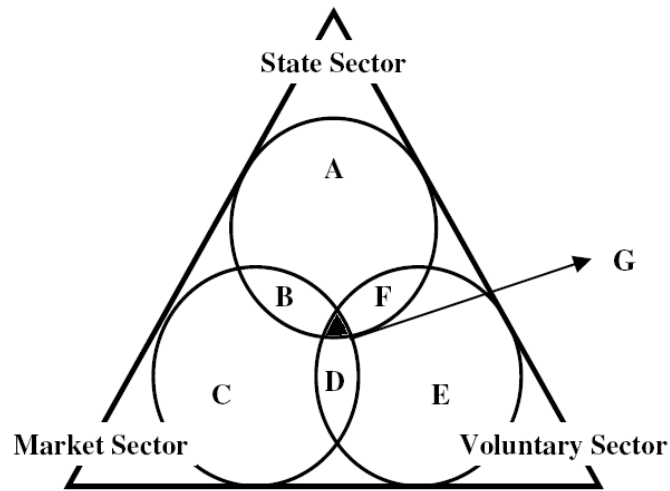


Figure 1.4: Picciotto Model (From [20]). G corresponds to the shaded area in the middle.

Mini legend: Area A represents public- or state- sector produced public goods; the market sector, area C, produces private, market goods; and area E, the voluntary sector/civil society groups, produces common pool goods. Overlap area B public, or regulated private corporations, produce toll goods, overlap area D, non-governmental organizations (NGOs), produce civil goods; overlap area F, hybrid organizations, produce public goods. For more details refer to section 3.2.2.

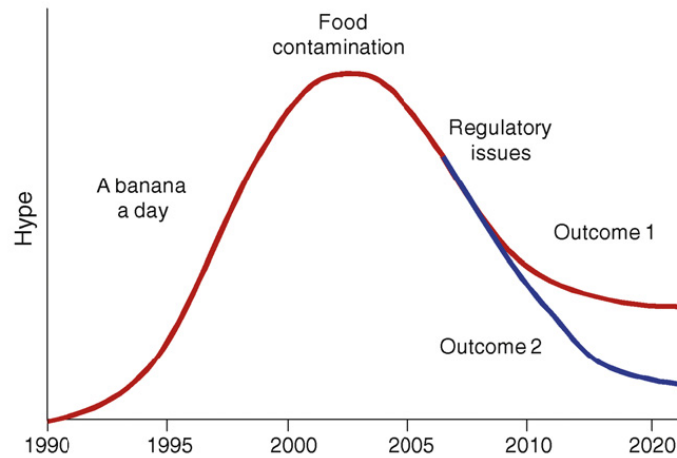


Figure 1.5: The PDV Hype Curve (From [14]).

The “hype curve” has been used to track public perception and sentiments around PDVs [14]. This curve (Figure 1.5) shows shifts in publicity generated around PDVs as a function of time. Favourable publicity up until early 2002 was fuelled largely by the idea of edible vaccines [11], as shown by the rising curve. This rise was brought down by fears of contamination of the food chain, and diminished further with concerns about regulatory problems and the lack of success and further development. Two outcomes are predicted: Outcome 1 represents the view of the future—a possible toned-down version of the pre-2002 era hype. The original concept of cheap edible vaccines has given way to a realization that there is a need for formulated products that may be injectable to be produced in clinical good manufacturing process (cGMP) facilities [16]. This transformation can be considered a practical compromise between the ideal world and the real world restrictions. Outcome 2 represents what might happen if industry and governments do not take up the technology: the hype will die away to levels that may make it very difficult in terms of public sentiment and negativity to fund any future plant-based production platform, however useful these may be [14].

Another aspect of the social issue is the emerging public resistance to immunization and vaccines. Dr. Lorne Babiuk, a prominent Canadian immunologist and vaccine expert indicates the presence of significant anti-vaccine lobby that links autism to immunization [22]. In an interview [23], Dr. Babiuk describes the lobby to be comprised of a variety of interest groups with a ‘fluid’ approach in generating momentum against vaccines. An example in this case is the lobby joining forces with the religious right to oppose HPV vaccine in Canada. Dr. Babiuk’s prediction is supported by the drop in HPV vaccination rates in ON and the prairie provinces occurring concurrently with religious groups’ and social commentators’ opposition to it [24]. Media reports about the fear of vaccination and the rumours fuelling the fears are spilling over into the developing and underdeveloped countries, causing setbacks to immunization programs in regions where mortality- and morbidity-due infectious diseases are a major concern [25]. Dr. Gregory A. Poland is Director of Mayo Vaccine Research Group at the Mayo Clinic and Foundation, and a member of the steering committee of the US National Network for Immunization Information. In his public discourse, he explores the concepts of innumeracy and denialism as archetypes that explain the dominant modes of thinking by anti-vaccine proponents [26]. Dr. Poland’s group is involved in developing and testing novel vaccines, understanding the genetic “drivers” of immune response to viral vaccines, and developing biological defence vaccines. Development and testing of such novel vaccines need regulatory oversight which has been discussed below.

1.2.3 Regulatory Issues

It has been suggested that PDVs be grown in an agricultural setting to take advantage of full potential of the agricultural scale of production. But as with any GM crops grown in the fields, there are regulatory issues that arise, including pollination and cross-pollination, and containment of such plants [27]. Introduction and adoption of disruptive technologies involve certain risks and associated liabilities. Failure to contain the flow of genes would result in regulatory liability involving the regulatory agencies, industry organizations, and civil society groups. If the public perceives the resulted liabilities to be linked either directly or indirectly to the innovative product, consumers will be less likely to purchase the product [21]. Topics that are discussed in this subsection include trust in regulatory institutions, the current post-marketing surveillance program for drugs and vaccines in Canada, and suggestions to build trust in regulatory institutions.

Stuart Smyth's doctoral thesis [21] elaborates on the management of potential GM liability issues, including those surrounding PDVs. Smyth presents the growing mistrust between the public and the industry, and he attempts to provide solutions to address this issue [21]. As PDVs are third-generation plant biotechnology products, it is important to learn about historical risks and liabilities associated with first- (agronomic qualities) and second-generation (product-quality characteristics) plant biotechnology products. Further reading about GM contamination and controversies is provided [30–38].

In Figure 1.4, area A represents regulatory agencies, area C, the industry organizations, and area E, the civil society groups. The overlap area of D between the civil society groups and industry is important in the commercialization and adoption of transformative technologies, and it is discussed later in this section.

The absence of two-way trust between society and the industry poses real challenges to the process of informed communication [21]. Consumers do not trust what the industry tells them, and the industry ignores consumers' demands, convinced their voices represent a minority of consumers. The institutional framework suggests that when there is a gap in the level of trust between industry and society, the only remaining stakeholder that can provide some basic level of reassurance in this situation is the regulatory agency [21]. In this case Health Canada fills this role.

Within the Health Products and Food Branch (HPFB) of Health Canada, post-market surveillance activities for all health products (GM and otherwise) is the responsibility of the Marketed Health Products Directorate (MHPD). MHPD reviews health product safety data, conducts risk assessments, and evaluates therapeutic effectiveness of marketed health products. MHPD can take appropriate action ranging from informing the public and health care community of new product safety information, to removing the product from the market, should a health product's safety, efficacy, or quality come into question [28].

It is therefore suggested that market surveillance and monitoring of GM crops (including PDVs) be undertaken by a multifaceted organization of industry, regulators, and civil society groups to provide a basic and solid level of confidence for these products, in an increasingly sceptical society [21], i.e., a shift from area A and C to overlap area G in Figure 1.4. Ways to instil consumer trust in the food safety system is speculated below.¹ Currently, only the Canadian Adverse Drug Reaction Monitoring Program coordinated by MHPD allows health care professionals and consumers to report adverse reactions within their post-market surveillance activities of health products [28]. The challenge identified in Canada is that the current science-based regulatory process has no official capacity to include comments or concerns from the consuming public [21]. Furthermore, previous attempts to incorporate the public's opinion have mostly provided unsatisfactory results in Canada [21].

Regulatory mechanisms are in place to ensure the introduction of only safe and effective products into the society and environment. These mechanisms should be balanced so

¹ The interaction of C and E is institutionally through civil courts and media (discussed in details in section 3.2.1). Smyth [21] also suggests the overlap D between firms C and the civil society E can also be occupied by agencies or independent third parties that are involved in testing for safety. According to their website [29], the Union of Concerned Scientists (UCS) is a leading science-based non-profit group working for a healthy environment and a safer world. UCS combines independent scientific research and citizen action to develop innovative, practical solutions and to secure responsible changes in government policy, corporate practices, and consumer choices. As UCS does independent scientific research in areas including food safety to author position papers for national policy development, they would be a good candidate to play a leading role in making food safety issues known publicly. An independent third party critical analysis (by groups such as UCS) of varieties approved, or in approval process by federal regulatory agencies, would make a positive impact in instilling consumer trust in the food safety system.

that innovation is not deterred by excessive regulations. The introduction of first-generation GM crops (agronomic qualities such as traits for biotic herbicide resistance and abiotic stress tolerance) serves as a good example to illustrate this challenge. The rigours of the regulatory requirements, in terms of the costs associated with conducting studies necessary to meet the demands of the regulators (for aspects such as gene flow, allergenicity, and toxicity) have been pushing public researchers out of the variety-development industry [39]. Public research institutions take a serious blow in this situation because they have limited budgets and simply do not have the finances to undertake the expensive research required to satisfy regulators. This situation necessitates commercialization of new varieties to be only performed by large multinational developers, thereby having a potentially large negative impact on the continuing development of varieties that are best suited for public good in Canada and abroad.

1.3 Objective

The primary objective of this research project is to explore whether a small- and medium-sized enterprise (SME) partnership would be a good business model for the introduction and adoption of PDVs. In the kind of business model under investigation, a research-intensive privately or publicly traded biotechnology SME usually forms public–private partnerships (PPP) in research networks, and strategic partnerships with large pharmaceutical/biotechnology companies for manufacture and/or distribution. The concept of PPP is described in section 2.2.4.

1.4 Method

Research into the adoption and governance of transformative technologies for social benefit crosses boundaries of traditional disciplinary studies. Interdisciplinary discourse allows the multi-perspective flow of ideas and access to researchers from a variety of disciplines. Research in this thesis builds on disciplinary knowledge and frameworks from the traditional areas of science, social sciences, and applied economics/business to answer the broader research questions. The thesis uses scientific papers for about 25% primary references and publicly available sources for the rest. Figure 1.6 illustrates the interrelation between the key elements.

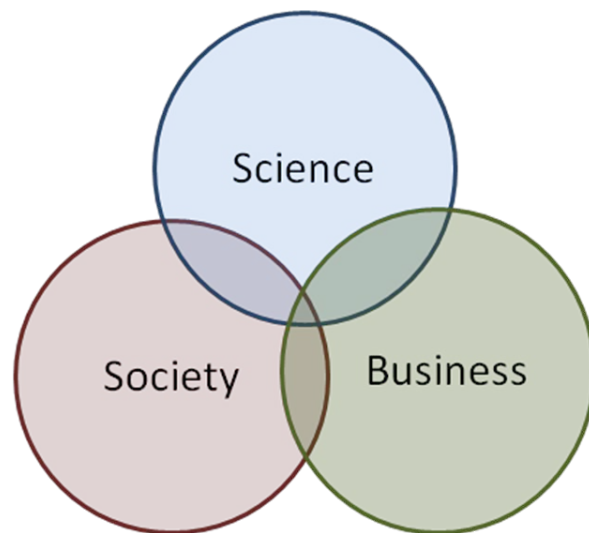


Figure 1.6: Spheres of Interdisciplinary Research.

This interdisciplinary research project takes the following approach:

- Understanding the scientific principles and advancements behind vaccines and life sciences/biotechnology.
- Gaining a basic understanding of economic frameworks in the areas of knowledge generation and use [40] and organizational forms [41]. Non-economic dimensions of

networked knowledge are also included. Background knowledge in markets and industry analysis for vaccines is included.

- Background reading in social responsibility, dynamics, and acceptability.

Special emphasis has been placed on the detailed study of issues of governance and IP mechanisms because of the transformative/disruptive nature of PDV innovation and its potential in terms of benefiting the broad focus and interest of the society.

1.5 Structure of the Thesis

Chapter 2 will present a review of the institutions involved in vaccine innovation. In Chapter 3, socio-economic models attempting to depict the process of innovation are reviewed. This is followed by a discussion of types of knowledge, economics of transactions, and non-economic dimensions of networked knowledge. Emphasis is on theoretical frameworks developed by Alston, Norton, and Pardey [40] (economic), and Mahoney [41] (organizational form).

Chapter 4 presents a critical analysis of PDV innovation through the examination of two biotechnology business case studies illustrating phases of development within the theoretical frameworks from Chapter 3. The generation and use of knowledge, the agreements secured to administer, and the institutional structures that facilitate each phase are presented within the two biotechnology business case studies. Chapter 5 concludes research findings and discusses policy implications for governments and the industry.

1.5.1 Positioning of the Thesis

The thesis attempts to understand and facilitate the adoption of PDVs for social benefit globally and access to vaccines in developing countries. It has been widely acknowledged that new vaccine innovations, including PDVs, have usually originated in developed countries.

Developing countries struggle regularly for access to basic public health, nutrition, education, and medicines. Popular policies in developed countries have focused on ensuring access to medicines (e.g., CAMR, see section 2.3) and basic public health in the developing and underdeveloped countries. Mechanisms of ensuring access, including humanitarian licensing and technology transfer, are discussed in section 2.3.

A hypothetical socio-economic case study was done in 2009 by Castle et al. [42] of a PDV (against Hepatitis B) technology diffusion model in India. It was suggested in the study that institutional hurdles to a widespread diffusion of the technology was an impediment that still needs to be overcome. The first step in overcoming the hurdles (above) would be R&D, licensure, and production of a pioneer PDV in a developed country (e.g., Canada and the USA). Each of these steps include generation and use of knowledge, economic transactions, and non-economic knowledge networking. Understanding these knowledge transfers, economic transactions, and institutional structures that facilitate each phase in this thesis would benefit the streamlined development of technologies and production of PDVs in Canada and the USA, thus potentially overcoming institutional hurdles to a widespread diffusion of the technology. The next step in realization would be extending the above understandings to developing countries where it is anticipated that PDVs will be adopted.

Building on the above work, this thesis is a first-known research compilation that analyzes the institutional structures and transactional forms in order to streamline development of technologies and production of PDVs in two industrialized countries: Canada and the USA.

A detailed analysis and discussion of the regulatory environment for potential PDVs presented could serve as an important resource for academic, government, and industry discourse. A

discussion of the social aspects of vaccines and GM crops with implications for PDVs makes this portion of the thesis uniquely interdisciplinary.

2. BACKGROUND

This chapter presents a review of the science and technology behind the development of PDVs, including the historical background, current developments, leading technology developments, and new concepts. Later, a review of the Canadian institutions involved in vaccine innovation and adoption is conducted, including examining public, private, and public—private partnerships, and drawing on specific examples from the PDV world. Vaccine introduction and adoption models in developing and underdeveloped countries with implications for PDVs are outlined in section 2.3.

2.1 Science and Technology Involvement in PDVs

With the PDV research concept having been proven, and with promising products having been created, a 2008 publication [12] presented the advantages of the PDV platform over conventional vaccines, and the challenges of introduction of PDVs to complement current vaccine manufacturing shortages. It was concluded that the remaining scientific and technological challenges being surmountable, the successful strategy for PDVs would have to rely on continued public support as an investment in the public good. It was also suggested that the move beyond the proof of concept would prepare the groundwork for the expeditious licensing of a pioneer PDV and would catalyze the prerequisite paradigm shift.

2.1.1 Historical Background

Originally, Drs. Guy Cardineau and Roy Curtiss III at Washington University in St. Louis, MO, developed the priority setting IP for oral immunization by transgenic plants, and, on 1 June 1995 [43], filed one of the first US patent applications[43] [personal communication, Dr. Cardineau,

11 September 2008]. Partly financed by a small start-up agricultural biotech company, Dr. Cardineau and Curtiss collaboratively developed oral delivery vaccines by transforming tobacco leaves to express the SpaA (surface protein antigen A) gene from *Streptococcus mutans*. A consortium of researchers, including Drs. Cardineau and Curtiss, from the Biodesign Institute at Arizona State University (ASU) had been working with Dow AgroSciences on a project to develop a plant-based gene expression technology to produce proteins that would serve as antigens in vaccines. Later, in 2006, a poultry vaccine against Newcastle disease virus (NDV) was successfully demonstrated to be safe and effective, and thereafter was approved by the US Department of Agriculture (USDA) [44]. The vaccine was developed at the Animal Health Unit of Dow AgroSciences in collaboration with researchers from Washington University, the Boyce Thompson Institute for Plant Research, and Benchmark Biolabs, Inc. [44]. This was the world's first PDV to get approval for commercial sale. By obtaining approval for the first PDV, Dow AgroSciences demonstrated that this new technology fits within the existing USDA Center for Veterinary Biologics regulatory approval process [12].

2.1.2 Current Developments

Initially, PDVs were developed to be taken orally (e.g., US patent 5,686,079 [43]) in order to avoid expensive cold chains and to be easier and safer than injection. As risk of tolerance induction in humans became pronounced [7], and in an effort to conform to strict pharmaceutical regulations, researchers later added processing techniques (e.g., freeze-drying) and measured dosage to their downstream processes and delivery SOPs.

Since 2000's PDV expression systems have included stable transgenic or transplastomic plants or plant cell lines, with inducible or constitutive expression, seed specific expression, and plant virus-based and *Agrobacterium tumefaciens*-based transient expression systems [16]. Based on the principal reasoning that PDVs stimulate the immune response at the mucosal level, researchers have been targeting diseases that infect through the mucosal system, including tuberculosis, pneumonia, influenza, diarrheal diseases, sexually transmitted diseases, and HIV, in the hope that PDVs could be especially effective against them [12]. Antigens from a variety of sources, including viral (e.g., HBsAg, HIV), bacterial, enteric pathogens (e.g., Enterotoxigenic *E. coli* heat labile toxin B), non-enteric pathogens, and self-antigens (e.g., immunocontraceptives) have been expressed in plants.

In terms of production economics, the magic number for protein yield is often estimated as 1% of the total soluble protein; however, this is seldom reached [14].

2.1.3 Leading Technological Innovations

Some leading innovations in PDVs have been reviewed [14, 16, 45]. Types of plants and plant tissues used for the production of protein and other vaccine antigens include the following: leaf and stem tissues of tobaccos of various species and varieties, *Arabidopsis thaliana*, alfalfa, spinach and potatoes; aquatic weeds such as *Lemna* spp. (duckweed); seeds of rice, beans, maize and tobacco; fruits like tomatoes and strawberries; root vegetables like carrots; single-cell cultures of the algae *Chlorella* and *Chlamydomonas*; suspension cell cultures of tobacco and other plants; hairy root cultures derived from various plants via *Agrobacterium rhizogenes* transformation; and transformed chloroplasts of a variety of plant species [14].

Whereas classical transgenesis or nuclear transformation for expression have been historically prominent in PDV R&D, transplastomic and especially transformed chloroplast expression have also been in the limelight for some time. Chloroplast/plastid transformation technology has been suggested to be useful in terms of combating bio-terrorism, as seen from the high yields obtained, for example, of *E. coli* LT-B, *Cholera vibrio* CT-B antigens, *Clostridium tetanii* toxin Fragment C, and *Bacillus anthracis* (anthrax) protective antigen (PA) [16].

Although constitutive or “green leaf” expression is the easiest to engineer, problems have been reported of proteins interfering with plant development and creating difficulties in protein purification. Biolex Therapeutics claims that, under good manufacturing practice (GMP) conditions, their “LEX SystemSM,” a simple commercial whole plant transgenic expression system using the common duckweed, *Lemna*, allows rapid product development due to ease of regeneration and rapid growth [14].

A comparison of different kinds of production platforms for biological products (proteins) is presented in Table 2.1. Compared to whole-plant systems, transgenic single cell cultures offer the advantages of a high level of containment, but lower yields [14]. Additionally, transgenic single cell cultures provide the possibility of producing proteins in bioreactors under GMP conditions, as is currently the case with conventional fermentation or cell culture techniques [14].

Table 2.1: Comparison of Different Biological (Protein) Production Platforms (from [45]).

The table illustrates a comparison of different platforms sorted by benefits (columns) and system complexity (rows). While our ranking places, for example, “overall cost” benefit ahead of “contamination risks,” some researchers may use an alternative ranking according to their purpose.

| System Complexity | Production System | Properties/Benefits (Increasing Importance from Left to Right) | | | | | |
|-------------------|------------------------|--|----------------------|-----------------------------------|------------------|-----------------|-------------------|
| | | Overall Cost | Production Timescale | Contamination Risks | Scaleup Capacity | Product Quality | Glycosylation |
| Bacteria | | Low | Short | Endotoxins | High | Low | None |
| Yeast | | Medium | Medium | Low risk | High | Medium | Incorrect |
| Non Transgenic | Plant cell culture | Medium | Medium | Low risk | Medium | High | Minor differences |
| | Mammalian cell culture | High | Long | Viruses, prions and oncogenic DNA | Very low | Very high | Correct |
| Transgenic | Plants | Very low | Long | Low risk | Very high | High | Minor differences |
| | Animals | High | Very long | Viruses, prions and oncogenic DNA | Low | Very high | Correct |

2.1.4 New Concepts

In transient expression systems, recombinant virus or other means are used to infect whole plants or plant cells to induce expression of foreign proteins. Thus the concept is offering the possibility of high level of expression of heterologous recombinant proteins in a relatively short time (due to the high copy number of plant viruses) [14, 44]. A combination of VLP-based (introduced in 1.1.2) antigen presentation and transient expression for production has been indicated as the driver of a rapid and low-cost vaccine production system at Medicargo Inc. (more details in subsection 4.3.1 IP Protection). In addition, novel adjuvants and delivery systems are also being developed to complement the emerging vaccines [44].

2.2 Institutions Engaged in Vaccine Innovation and Adoption

This subsection outlines the various institutions involved in vaccine innovation, introduction, and adoption in Canada. These institutions are most likely to get involved in PDV innovation and the anticipated adoption in Canada. The institutions engaged in vaccine innovation and adoption are best approached by referring to Picciotto's model in Figure 1.4, where A represents the public or state sector, C, the market sector, and E, the voluntary sector. The following discussion will mainly focus on the Canadian innovation scenario, with parallels drawn from the USA and Europe whenever possible and necessary. Canadian Institutes of Health Research (CIHR) have reviewed the organizations involved in vaccine innovation and adoption [46] in Canada and their review is presented in the paragraphs further below.

To better understand the role of institutions involved in vaccine innovation and adoption, the concept of push and pull forces shaping vaccine innovation is appropriate. In the context of vaccine innovation and introduction, push forces are principally composed of scientific and technological advances, management, and coordination support, and the availability of research and product development funding [59]. Conversely, pull forces are represented by governments and the public sector recognizing and making commitments to the fulfillment of public health needs and the potential profitability of a future product within a specific market segment [59]. As these mechanisms are synergistically coupled, investment in either and/or both has positive effects on the entire vaccine innovation process. In the vaccine industry, the push forces, namely technology, management, and funds are integrated by company operations to target either existing or emerging markets. For publicly funded vaccine research, discrete mandates of numerous independent entities add a layer of complexity in achieving objectives [59]. Technology, research and product development funds, and management constitute the push factors; management and procurement funds availability, control priorities and health systems capacity, and advocacy constitute the pull factors. Some of these forces are explained below (see also Figure 2.1a from [59]).

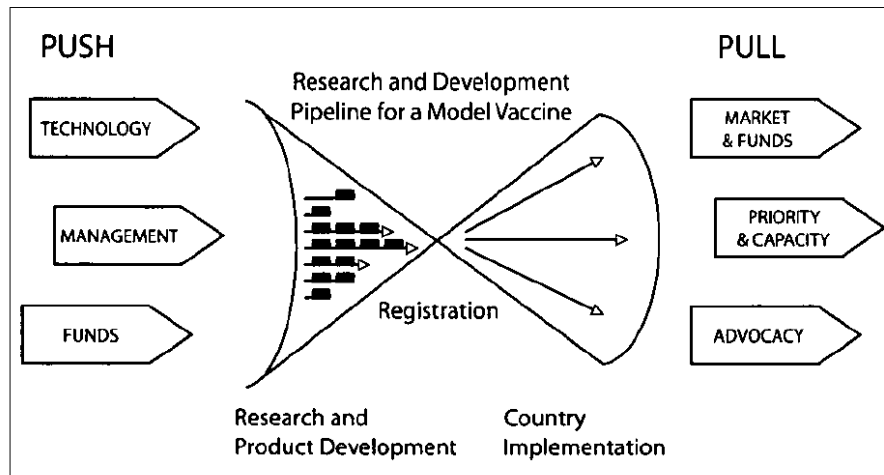


Figure 2.1a: Push and Pull Forces in Vaccine Innovation (from [59]). The arrows inside the cones represent the movement along the Push and Pull continuum. Black boxes represent potential vaccine candidates that will eventually yield one licensed product.

Technology push: Several publicly funded research funding entities—including the US National Institutes of Health (NIH), Canadian Institutes of Health Research, the US Medical Research Council, the US Agency for International Development (USAID), the WHO Initiative for Vaccine Research, the United Nations’ Children’s Fund (UNICEF)/ United Nations Development Programme (UNDP)/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, the Program for Appropriate Technology in Health, and the International Vaccine Institute—are actively involved in the technology push. These networks build on their collective research capabilities to fight challenges in infectious disease–endemic countries [59].

The Pharma-Planta Project [110], a consortium of 39 principal scientists from academic and industrial institutions in Europe and South Africa, was funded by the European Commission in the area of “Plant platforms for immunotherapeutic biomolecule production.” Pharma-Planta was formed to build a plant-based production platform for pharmaceuticals in Europe and to enter the first candidate pharmaceuticals into human clinical trials. Their programme is anticipated to develop robust risk-assessment and risk-management practices based on health and environmental impact, and would work with EU regulatory authorities such as EMEA and European Food Safety Authority to ensure safety and acceptance. Members of the Pharma-Planta consortium recognized the need to develop scientific knowledge and products to specifically address the health needs of the poor in developing countries, and they have signed on to a Statement of Intent that promises to make the work from the program freely available for the achievement of humanitarian purposes [86]. For some results of this project, see section 5.3.1.

Research and product development funds push: Increased contributions from developed countries to developing countries have attempted to compensate for the insufficient public spending on research and product development in public health tools and vaccines in developing countries. These contributions have been in the form of funding from bilateral development agencies, including the following: state aid agencies, including USAID, the Canadian International Development Agency, the United Kingdom’s Department for International Development, and the Swedish International Development Agency; multilateral organizations, including WHO, the UNDP, the World Bank, and the European Commission; and public and private foundations and grant support programs, including NIH, the Rockefeller Foundation, the Wellcome Trust, and the Bill & Melinda Gates Foundation [59]. The Bill & Melinda Gates

foundation (Global Health Program) supports accelerating the introduction of new and underused vaccines [44], including PDV research [111]. The European Commission's five year funding of Pharma-Planta as part of the Sixth Framework Programme is an example of a push factor in PDV innovation. GAVI Alliance has both pull (below) and push force mechanisms. GAVI Alliance is a PPP created in 2000 to save children's lives and protect people's health by increasing access to immunization in poor countries [112]. Its partners include national governments, UNICEF, WHO, the World Bank, the Bill & Melinda Gates Foundation, the vaccine industry, research and technical health institutions, and civil society organizations. GAVI Alliance's public financing commitments are obtained from governments and the European Commission. Private financing adding to its start-up grant is obtained from the Bill & Melinda Gates Foundation. As a push force, GAVI resources are used to research the prospects of accelerating the development and introduction of vaccines against two diseases, rotavirus and pneumococcus [112]. These diseases are responsible for significant mortality in developing countries. GAVI pneumo-AMC is a result of donations from countries and a private philanthropic foundation subsidizing vaccine development and production (for details, see 2.3). The push mechanism of research and product development funds available for vaccine candidates to combat infectious diseases in a global context with a focus on affordability perfectly fits PDV objectives.

Management push: Good management of time and resources is important for the success of vaccine innovation and introduction. As discussed above, many of the international initiatives, public-private partnerships, and alliances created are active in vaccine research and product development. Some of these, including the Aeras Global TB Vaccine Foundation, the International AIDS Vaccine Initiative, and Program for Appropriate Technology in Health's

Malaria Vaccine Initiative, have been created specifically to manage product development processes and are focused on single diseases [59].

Market and procurement funds availability pull: Capital expenditure barriers resulting from the need to produce vaccines in accordance with good manufacturing practices have led to current practices of publicly funded vaccine research and product development to partner with at least one industrial partner, or, at a minimum, one established manufacturing entity [59]. Factors that have an impact on the minimum level of pull forces necessary for attracting significant funding from an industrial partner are independent of the jurisdiction (developing vs. established market economy) where the products will be introduced; the factors include developmental and commercialization costs and risks, which result in the risk-adjusted chance of generating acceptable stakeholder return from a finite budget [59]. A potential solution to this dilemma is public sector increases in procurement commitments and funding; this approach has been observed to be successful in attracting commercial entities to invest in the development and production of the relatively low-cost HBV [59]. As vaccines are losing their reputation for being low-profit, high-risk biological products, and in light of large pharmaceutical companies losing profits to competition from generics, drying product pipelines, and increased regulation and costs, private companies are now turning to strengthen their vaccine candidate pipelines [9].

Control priorities and health systems capacity pull: Public sector entities, such as international organizations and disease control programs, providing national governments with sufficient information about disease burden and the cost-effectiveness of new vaccines, will allow national governments to include evidence-based decisions about the introduction of new

vaccines in their immunization programs; this clearly presents a pull factor to stimulate vaccine research and product development [59]. Some WHO programs are considered to be a part of this pull force, as illustrated below.

Malaria vaccines are the most cost-effective interventions to reduce the enormous burden of disease in the poorest countries of the world. For commercial development, the industry initially was not willing to commit resources because of perceived minimal market return. In order to assemble an adequately resourced public sector effort, in 1999 the WHO coordinated a meeting of international group of experts, including scientists, representatives from industry, and some major funding agencies. The meeting was funded by WHO's Tropical Disease Research (TDR) and by Training and Roll Back Malaria (RBM), the Bill & Melinda Gates Foundation, and the US NIH (NIAID and the Fogarty International Center). The purpose of the consortium (pull) was to develop safe and effective transmission-blocking vaccine candidates to the point of "proof of principle" to induce industrial commitment to vaccine production [113].

PREVENT, an incorporated Canadian non-profit organization located in Saskatoon, is driving control priorities and health systems capacity pull. PREVENT conducts pre-clinical and clinical trials for promising early stage vaccine candidates, fast tracking critical mid-stage vaccine development for diseases of major concern to public health, and reducing the risk factor for investors and potential receptor companies [114]. Policy implications of PREVENT are discussed in section 5.2.1.

GAVI Alliance provides time-limited funding (usually over five years) for the supply of vaccines and other forms of support to strengthen health systems and immunization services in countries where GAVI Alliance programs are implemented [112]. This is done in order to save children's lives and protect people's health by increasing access to immunization in poor countries.

Advocacy pull: It has been observed that evidence-based advocacy can have a great impact on attracting the attention of researchers and funding bodies for vaccine development projects [59]. The AIDS Vaccine Advocacy Coalition (AVAC) provides an example of an international non-profit organization that uses education, policy analysis, advocacy, and community mobilization to accelerate the ethical development and eventual global delivery of AIDS vaccines. MSF, Oxfam (for details, refer to subsection 2.3) and Universities Allied for Essential Medicines have advocated globally for access to affordable vaccines in developing and underdeveloped countries.

In conclusion, a balance of synergistically coupled push and pull factors is important for a sustainable PDV vaccine pipeline. Commitments and collaboration are required from the governments, voluntary sector, and private companies for the expeditious introduction of high-priority life-saving vaccines.

2.2.1 Institutions

It is to be acknowledged that BIOTECCanada's Vaccine Industry Committee (VIC) has become a voice of the Canadian vaccine industry. It is equally important to indicate that some important information in the following sections primarily obtained from VIC's publicly available research

paper [47], may be biased and/or strongly favoured towards representing the interests of the industry.

The vaccine introduction process is illustrated in Figure 2.1 (from [47]). This section attempts to map the institutional structures involved in vaccine R&D, innovation, introduction, and regulation in Canada. In Canada, as in most developed countries, the following initiatives have to be taken for successful incorporation of a new vaccine into a national immunization program [47]: establishing medical need, and demonstrating safety and efficacy (or immunogenicity) in clinical trials; obtaining marketing authorization (regulatory approval) for commercial launch; developing national recommendations for optimal use; securing funding to support vaccine program delivery; and providing necessary infrastructure for vaccine program implementation. These initiatives should be executed via the following processes: ensuring adequate vaccine supply and distribution capacity; assuring education of (and acceptance by) the public and medical community; establishing an appropriate infrastructure for vaccine distribution and delivery; and monitoring vaccine use, safety and effectiveness through post-market studies.

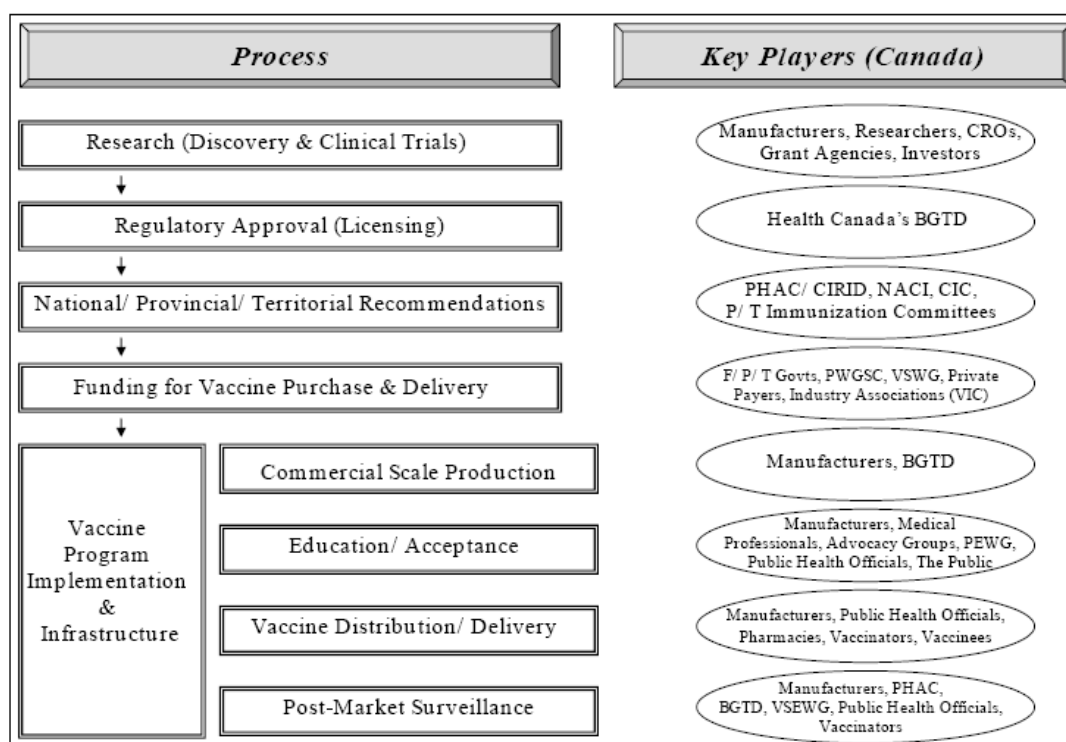


Figure 2.1: Vaccine Introduction Process into the Canadian National Immunization Program (From [47]). The blocks on the left represent the steps involved in vaccine introduction and the ellipses on the right represent the corresponding institutions involved in the step. Subsection 2.2, especially subsection “National Immunization Program” outlines details about the institutions involved in vaccine innovation, introduction, and regulation. The acronyms are as follows: BGTD, Biologics and Genetic Therapies Directorate; CIC, Canadian Immunization Committee; CIRID, Centre for Immunization and Respiratory Infectious Diseases; CROs, Clinical Research Organizations; F/P/T Governments, Federal/Provincial/Territorial Governments; NACI, National Advisory Committee on Immunization; PEWG, Professional Education Working Group; PHAC, Public Health Agency of Canada; PWGSC, Public Works and Government Services Canada; VIC, Vaccine Industry Committee; VSEWG, Vaccines Safety Expert Working Group and VSWG, Vaccine Supply Working Group.

2.2.2 Public Institutions

Many federal government departments, publicly funded research institutions, and universities are involved in vaccine innovation and adoption in Canada, and some have even contributed to various R&D projects involving plants as a platform technology [46]. This subsection has been divided into research and development, and regulatory based on the duties and services public institutions provide.

Research and Development: Agriculture and Agri-Food Canada (AAFC) was involved with the Canadian Department of National Defence (DND) in expression and processing of influenza and encephalitis vaccines in plant cells [12]. Defence Research and Development Canada (DRDC), DND, performs research and develops technology for national security that includes research on and acquisition of vaccines against organisms that could be used in biological warfare. Their vaccine-related research priorities include novel platforms for rapid post-exposure immunization and broad spectrum vaccines. DRDC is also responsible for advanced development, support for Canadian licensure, and acquisition of initial stockpile of vaccines.

The Centre for Immunization and Respiratory Infectious Diseases (CIRID) of the Public Health Agency of Canada (PHAC) collaborates with the provinces and territories, other federal departments, and other entities to prevent, reduce, or eliminate vaccine-preventable and infectious respiratory diseases; reduce the negative impact of respiratory infections; and maintain public and professional confidence in immunization programs. PHAC National Microbiology Laboratory performs reference microbiology and surveillance, provides support to epidemiology

programs, and conducts applied and discovery research, including research for vaccines against pathogenic viruses and bacteria.

National Research Council (NRC) of Canada's vaccine research priorities include adjuvants, immunomodulation, and vaccine delivery; glyco-vaccine strategies for childhood diseases; and vaccine strategies for intracellular pathogens. The NRC Institute for Biological Sciences is engaged in research focused on infectious diseases, cancer vaccines, immunotherapeutics, and neurodegenerative diseases. About 60% of the research is directed towards discovery of new vaccine strategies.

Vaccines and Infectious Diseases Organization (VIDO), located on the University of Saskatchewan campus, is a vaccine-research organization that operates with support from the governments of Saskatchewan and Alberta, the Government of Canada, foundations, and industry competitive grants. VIDO, the Canadian Center for Vaccinology (a partnership among Dalhousie University, the IWK Health Centre, and Capital Health) in Halifax and the UBC Centre for Disease Control have a history of collaborative R&D and testing of vaccines, such as the SARS Accelerated Vaccine Initiative and the maternal immunization against pertussis project. These institutions are the R&D partners of the Pan-Provincial Vaccine Enterprise (PREVENT, see section 2.2.4).

Basic vaccine research in Canada is funded by major research funding agencies, including the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council (NSERC), the NRC Industrial Research Assistance Program of Canada (IRAP), the Canada

Foundation for Innovation, the National Cancer Institute of Canada, and the Canadian HIV Vaccine Initiative (CHVI). CHVI is a collaborative undertaking between the Government of Canada and the Bill & Melinda Gates Foundation [47].

Regulatory: Canadian Food Inspection Agency (CFIA) is a federal government agency reporting to the Minister of Agriculture and Agri-Food (AAFC). CFIA delivers inspection and quarantine programs related to foods, plants and animals which include supporting vaccine research and animal vaccination, which prevents the spread of disease to humans. CFIA is involved in regulation of novel biotechnology products, including those based on plants. CFIA's Plant Biotechnology Office is responsible for environmental release of plants with novel traits (PNT) intended for plant molecular farming (PMF) [12]. CFIA regulates these products for confined and unconfined environmental release under the *Seeds Act* and the *Seeds Regulations* (Part V), and safety assessment for use of by-products as feed is carried out under the *Feeds Act and Regulations*. The US equivalent in this case for the oversight would be the USDA Center for Veterinary Biologics.

The Health Products and Food Branch (HPFB) of Health Canada is responsible for regulating PDVs under the *Food and Drug Act* and is usually involved during clinical trials and pre- and post-marketing of biological products [12]. Vaccines are regulated as a subset of drugs known as biologics (i.e., derived or prepared from living organisms), and the Biologics and Genetic Therapies Directorate (BGTD) within HPFB reviews and approves all vaccines authorized for sale in Canada. Health Canada also supervises all aspects of vaccine production by manufacturers to ensure safety, sterility, and quality of large-scale batches or “lots” [47]. The US

equivalent for federal oversight would be the U.S. Food and Drug Administration (FDA), and in the EU, the European Medicines Agency (EMA). The National Immunization Program illustrates the introduction of new vaccines in Canada and is discussed below.

It has been noted at public conferences that PDVs have been produced and clinically tested under the US investigational new drug application (IND), and all applicable regulatory and GMP requirements are in place for this type of product [48].

National Immunization Program: An introduction of new vaccines into the Canadian national immunization program has been reviewed [47] and illustrated in Figure 2.1 (from [47]). Regulation and oversight of the vaccine industry is done by Health Canada as the federal regulatory authority, and the PHAC as the lead body in overseeing immunization evaluation and recommendation processes. Although official vaccine recommendations are made at the national level, decisions regarding the integration of new vaccines into publicly funded immunization programs are primarily a provincial/territorial responsibility carried out by Provincial/Territorial Immunization Committees. CIRID oversees the relevant expert groups that guide immunization procedures within the existing PHAC structure. These expert groups, including the National Advisory Committee on Immunization (NACI) and the Canadian Immunization Committee (CIC), collectively known as the Public Health Network, report to the Federal/Provincial/Territorial (F/P/T) Conference of Deputy Ministers of Health. A new vaccine is subject to the scrutiny of NACI after being approved by the BGTD. NACI is the national expert body that uses evidence-based methods to assess whether the vaccine should be used, and it provides

scientific recommendations for vaccine use in Canada to target groups that will most benefit from inoculation. All of NACI's recommendations are publicly available. CIC, a relatively newer committee, is comprised of vaccine program representatives from the F/P/T ministries of health. The vaccine industry group, BIOTECanada VIC's viewpoint on the vaccine introduction process is below.

“...For the past five years particularly, federal funding has played a key role in financing vaccine programs in Canada, notable through the Canadian Immunization Trust Fund...

...Administered by Public Works and Government Services Canada (PWGSC) and overseen by the VSWG subgroup of the CIC, most of the vaccines used in publicly funded immunization programs are purchased through a bulk purchasing program. (According to BIOTECanada VIC) vaccine purchases must follow an open, fair, and transparent procedure - respecting Canada's obligations under applicable national and international trade agreements ...” [47]

It is argued by BIOTECanada VIC that the potential overlap between BGTD and NACI review procedures in introducing new vaccines in Canada, and the involvement of several duplicative procedures in the current recommendation process (BGTD, NACI, and CIC) for public vaccine programs in Canada can potentially contribute to delays in access to innovative vaccine products by patients [47]. Correspondingly, the industry's need for faster and more transparent vaccine approval in Canada has been identified in a CIHR survey [46]. The survey revealed that the cause of this problem might be partly due to under-funding of regulatory groups, and in response, it has recommended a better working engagement of the industry representatives with the scientists and clinicians of public health regulators. The

federal/provincial responsibility divide in vaccine recommendation, planning, funding, and delivery programs has also been identified by BIOTECanada VIC to be straining scarce human and financial resources within Canada's immunization infrastructure [47].

The federal government also oversees both passive and active national vaccine surveillance systems. The Canadian Adverse Events Following Immunization Surveillance System (CAEFISS), a passive surveillance system that collects reports from health care providers on adverse events following immunization, is coordinated and supported by PHAC. The Immunization Monitoring Program ACTive (IMPACT) is an active surveillance system for documenting adverse events following immunization through 12 pediatric hospitals across the country. The BGTD and PHAC/CIRID have authority to decide upon the best course of action for resolution if unexpected or increased side effects due to vaccines occur within the IMPACT system.

2.2.3 Private Companies

The market sector (C in Figure 1.4) is entirely represented by the vaccine industry.

BIOTECanada consists of representatives from small- and medium-sized biotechnology enterprises and core multinational companies, including vaccine developers and producers [46].

VIC is a subcommittee of BIOTECanada consisting of industry representatives who have a focus to create a vaccine environment conducive to the goals of public health and manufacturers [46].

The large vaccine companies, namely GlaxoSmithKline (GSK) Inc., Merck & Co., Inc., Sanofi Pasteur, Novartis, and Wyeth Canada (acquired by Pfizer Inc.), have dominated vaccine R&D and manufacture in Canada. Medicago Inc., a Canadian SME in the forefront of PDV innovation,

is a subject case study of this thesis (see Chapter 4, section 4.3.1). The private vaccine research community consists of the discovery and clinical research departments of the lead (first and second tier) industry players mentioned above, including several other SMEs [47]. Sanofi Pasteur has a large-scale vaccine manufacturing facility (known as the Connaught Campus) based in Toronto, and GSK has vaccine production facilities in Québec City and Laval, Québec; these facilities supply vaccines for global clinical trials and/or commercial sales (e.g., for influenza and acellular pertussis vaccines, by GSK and Sanofi Pasteur, respectively) [47].

2.2.4 Public–Private Partnerships

Public–private partnerships (PPPs) are an arrangement of transaction (area B in Figure 1.4) between the public goods producing state and the market, a compromise between public good and private property ownership. From a development and public policy perspective, the following are the drivers of PPPs [49].

As the state pursues policies to maximize the interests of society altogether, governments or organizations look to collaborate with one or more partner(s) who share their particular objectives, e.g., poverty reduction. Once the partners have agreed on partnership objectives, the type of governance most suitable to the partnership must be examined. The governance structure provides a framework within which the partners can make strategic decisions (in relation to the partnership objectives), organizational decisions (regarding the use of financial and non-financial resources), and operational decisions (regarding the delivery of the partnership’s outputs) [49]. A written, but incomplete, agreement should then be made between the partners to recognize the importance of agreeing on ways to manage the partnership, such as IP and revenue management,

and conflict resolution. Written agreements between partners are considered incomplete because it is not possible to write agreements that predict all possible actions and events [49]. A partnership can thus be considered a joint effort towards common public policy objective(s), by means of shared governance based on incomplete written agreement [49].

In 1989, the federal government established the Networks of Centres of Excellence (NCE) to enhance partnerships between university and industry researchers. The NCE program is supported and directed by the CIHR, NSERC, and the Social Science and Humanities Research Council of Canada (SSHRC), and is in partnership with Industry Canada [50]. An integral part of Canada's Innovation Strategy, NCE networks are large-scale, academically led virtual research networks that bring together partners from academia, industry, government and not-for-profit organizations [51] to turn Canadian research and entrepreneurial talent into economic and social benefits for all Canadians. This type of relationship is in contrast to corporate partnerships, which are primarily profit-oriented. Building on the success of the original NCE program that funds research, the Centres of Excellence for Commercialization and Research (CECR) program supports the operating expenses of a centre, and the commercialization of such research [52].

PREVENT, one of the CECRs, is working with public health experts, the vaccine industry, and the investment community to move promising vaccines against diseases of major public health concern to the stage where they can be licensed to an industry partner for late-stage clinical trials and commercialization. PREVENT's institutional role in vaccine innovation pull has been highlighted in 2.2. The federally funded Genome Canada program, launched in 2000, and its projects, involves an array of PPP that were expected to contribute to pushing Canada into a

position as one of the world's most innovative countries by 2010 [53]. One of the objectives of the Genome Canada/Genome Prairie project entitled "Functional pathogenomics of mucosal immunity" was to determine the influence of vaccines and other agents on host gene expression in order to provide new information about the processes of disease and innate immunity to microbial pathogens.

R&D and testing efforts of the cytomegalovirus (HCMV) subunit vaccine in plant and plant parts involved a consortium from the University of Ottawa, Health Canada, the Canadian Red Cross Society, AAFC, Prairie Plant Systems Inc. and others [12]. This consortium shows a working example of a traditional model of state-private sector PPP (Health Canada, AAFC, and Prairie Plant Systems) working with public universities and NGOs (area D in Figure 1.4).

2.3 Vaccine Introduction and Adoption Models

Vaccines have been deployed in developing countries to combat infectious diseases. Cost effectiveness, safety, technology transfer, and scalability of PDV technology make it very attractive to be rapidly introduced and adopted in developing countries. Access and affordability, on the other hand, hinder the application of many currently available medicines in developing country environments [81]. Below is a selection of ways in which vaccines can be made accessible and affordable to developing and underdeveloped countries. Some of these models are applicable to PDVs.

Canada's Access to Medicines Regime (CAMR) was the first attempt in making Canadian drugs (including vaccines) accessible and affordable to developing countries, and it is documented here. In the late 1990s, Médecins Sans Frontières (MSF/Doctors Without Borders), Oxfam, and other NGOs commenced a public awareness campaign in which they identified patents as a principal barrier to access to medicines in developing and under-developed countries. Members of the World Trade Organization (WTO) who met in Doha in November 2001 unanimously recognized patents as being an important obstacle for developing countries wanting to access essential medicines. In 2003, the WTO adopted a "historic agreement" intended to permit developed countries to export generic versions of patented medications to developing countries. Responding to pressures from Canadian civil organizations and Stephen Lewis, the UN Special Envoy on HIV/AIDS in Africa, in September 2003, Canada became the first country to announce that it would amend its patent law to authorize the export of generic versions of patented medicines to developing countries. In May 2004, the Parliament of Canada unanimously adopted Bill C-9, known as the [Prime Minister] *Jean Chrétien Pledge to Africa Act*. The bill was unanimously supported by NGOs, pharmaceutical companies, and producers of generic medicines [82]. Canada's Research-Based Pharmaceutical Companies (Rx&D) continues to support the principles behind CAMR. In addition, preferential and non-profit pricing have been key initiatives used by Rx&D member companies to increase access to medicines in developing countries [83]. Study of CAMR is important, from a historical perspective, to learn about the success and failures (discussed in detail below) of an industrialized country specific model (and framework), created by federal legislation to make medicine (and vaccines) affordable for the developing and underdeveloped countries.

A different form of the access to medicines principles is proposed by a hypothetical case study done in 2009 by Castle et al. [42] for a PDV against Hepatitis B in India through a diffusion model case study. It was concluded that producing a PDV in the United States that is then distribution by an Indian firm in India is expected to yield the fastest time of distribution, and thus the greatest health benefits. It was also suggested that institutional hurdles to a widespread diffusion of the technology still need to be overcome. The members of the scientific community engaged in PDV activity recognize that in order for public sector groups to accomplish their public good objectives, they should use humanitarian licensing practices [15]. A process of two-tier licensing is suggested, whereby developed nations would pay regular price for vaccines. On the other hand, the license to developing nations would be arranged in a way such that ensures their poor population get access to these vaccines at a much reduced affordable price.

The Global Alliance for Vaccines and Immunisation Alliance's (GAVI) Advance Market Commitment (AMC) is a financing model that subsidises pharmaceutical companies for the development and production of new vaccines intended specifically for developing countries. The subsidy is only paid once a vaccine meeting certain specifications is made available at a given price set by the AMC donors. For pneumococcal vaccine AMC (pneumo-AMC; to prevent pneumococcal infections by *Streptococcus pneumoniae*), a candidate must meet WHO pre-qualifications and be available at US\$7 (2010 US\$ values) per dose price. Contributors of the US\$1.5 billion pneumo-AMC are Italy (US\$635 million), the UK (US\$485 million), Canada (US\$200 million), Russia (US\$80 million), and Norway and the Gates Foundation (US\$50 million each) [84]. The signing of supply agreements for pneumococcal vaccines within pneumo-AMC by Pneumo-AMC, and GSK and Pfizer has been criticized by MSF for price

affordability barriers, limited production and access (poorest countries only), and access contingent on registration in individual jurisdictions [85]. It is indicated that at a cost of US\$21 per child (three doses at US\$7 per dose), donors and GAVI will be spending much more money for a vaccine than the existing vaccines in developing countries [85]. Comparatively, UNICEF paid US\$2.80 for DPT–H influenza vaccine and US\$0.62 for HBV (2005 figures) [86]. Pneumo-AMC suggests a potential long-term cap price of US\$3.5 for pneumococcal vaccines in developing countries [76].

A model for two-tiered pricing exists. As part of GAVI pneumo-AMC, GSK will charge governments in poor African countries US\$7 per dose of Synflorix pneumococcal vaccine for use in public sector clinics, starting in December 2010 [87]. Europeans pay around €40 (US\$54) per dose for the same vaccine. This launch was controversial as MSF made a public report of GSK promoting its Synflorix pneumococcal vaccine to Ugandans willing to pay US\$50 per dose from their own finances [87]. GSK made a statement afterwards that it would reduce its prices in Uganda, acknowledging MSF had pointed out that a violation of GSK's tiered pricing policy.

Though viewed as a paradigm shift, CAMR has been largely been ineffective [88] in delivering its goals. It has been argued that delivery of CAMR policy has been a near total failure [89]. The law has only been used once and the Canadian company Apotex involved in the process found the separate negotiations for approval so burdensome that it promised never to use it again. Apotex's experiences and challenges operating within the framework of CAMR have been documented [88]. Recent parliamentary procedures aimed at amending CAMR have been reviewed [89, 90].

In a follow up to their position from late 1990s, in 2010 MSF and Oxfam warned that high prices and the currently acute funding crisis (at least primarily for GAVI; see section 2.2) would hamper the global approach to ensure access to life-saving vaccines for children in the poorest countries [91]. It was indicated that although the competition to achieve price reductions has been very effective for expanded program on immunization vaccines, the same has not yet been realised for the newest vaccines [92]. Prior experiences with tiered pricing, particularly for new vaccines, have been mixed and have not yet led to sustainable prices, either in low- or middle-income countries [92]. It is recognized the current market-based R&D system failed to address the need for improved, cheaper, and more suitable versions of existing vaccines [92]. Additional efforts to analyze, prevent, or remove patent barriers have been recognized to be necessary, including using open licensing policies on the parts of universities and government research bodies, and exercising the Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS Agreement) flexibilities when appropriate. To ensure vaccines meet the needs of developing countries in terms of presentations and serotypes, it has been suggested WHO prequalification and other mechanisms be used. It is remarked that only a handful of multinational pharmaceutical companies continue to produce the newest vaccines, whose oligopoly status allows them to charge high prices [91]. Despite GAVI's global role and negotiating power, the newest vaccines are inaccessible to the poorest countries due to high prices.

The TRIPS Agreement is an integral part of the World Trade Organization (WTO) Agreement [93]. The TRIPS Agreement makes it mandatory for countries to ensure that patent protection is available in all fields of technology, for both process and product inventions. The global introduction of the TRIPS standards is expected to delay the marketing of generic versions of new drugs, and, thus, the competition they entail [93]. It is anticipated by WHO that prices of newer drugs will remain high for a longer time due to TRIPS, which will result in reduced access for many people, notably in developing countries [93], thus seriously restricting access to medicines.

Recently, public health groups, humanitarian and intergovernmental organizations, experts, and academics that work on access to medicines gathered at the University of California at Berkeley on 15 July 2010, to issue the Berkeley Declaration on Intellectual Property Enforcement and Access to Medicines [94]. They identified that recent worldwide “intellectual property enforcement” initiatives threaten access to affordable medicines in poorer countries, and declared that responsible enforcement initiatives must not interfere with access to medicines and should be grounded in human rights principles; protect innovation, competition, and consumer rights; be negotiated through a transparent, inclusive, and open process that does not bypass existing multilateral institutions; and protect the full use of TRIPS flexibilities that promote access to medicines.

It has been suggested that, to achieve increased access to medicines, advantage be taken of TRIPS safeguards in terms of: (i) compulsory licensing, (ii) parallel importation, and (iii) provisions for early working [93]. The compulsory license safeguard is of special interest in the

context of this discourse. This is a license to use an invention that has been granted without the permission of the patent holder [93]. This license can be used to allow the production and sale of generic products before the expiry of the patent, thus increasing opportunities for competition, and eventually driving prices down. A special case of this licensing is “government use” (or a compulsory license for public non-commercial use) where TRIPS imposes less stringent conditions. However, it is indicated that the safeguards provided for in TRIPS can only be used when incorporated in national law [93]. Therefore, it is important that the compulsory license be included in public health policy and national legislation to protect the public interest and public health. Many countries, including many developed countries, have provisions for compulsory licenses in their national laws. The federal Department of Industrial Policy and Promotion in India is currently investigating the option of introducing compulsory licensing under the (Indian) Patents Acts to address the concerns about the availability of low-cost life-saving drugs [95].

Another working example of access to medicines is illustrated by the Developing Countries Vaccine Manufacturers’ Network (DCVMN), established in 2001. DCVMN is a voluntary public health-driven alliance of vaccine manufacturers owned by and located in developing countries that offer a consistent and sustainable supply of affordable and accessible quality vaccines [96]. In the beginning, DCVMN’s main strategic priority was to increase access to vaccines for HepB and Hib containing the diphtheria pertusis tetanus (DPT) combination. It was hoped at that time that GAVI would support DCVMN by push mechanisms, such as facilitating access to technology as DCVMN’s priorities were in line with objectives of GAVI. However, the expected support from GAVI Alliance at that time did not happen, partly due to international concerns for unfair subsidizing certain individual manufacturers. Some of the factors that secured support for

DCVMN are the transfer of conjugation technology from the Netherlands Vaccine Institute (NVI), the ability of the ‘‘receiving’’ DCVMN members to invest upfront in this conjugation technology, and their ability to absorb the transferred technology. Due to these support factors, the main strategic priority of DCVMN has nearly been reached at a global scale [96].

Serum Institute of India Ltd. (SIIL), a part of DCVM, recently acquired licenses for an indigenous monovalent Hib and for pentavalent (DTP—Hep B—Hib) vaccines [96]. SIIL obtained the NVI Hib process technology from the Netherlands Vaccine Institute. It is expected that SIIL will get the necessary clearance to supply vaccine to UN organizations, with a production capacity of over 100 million doses. It is anticipated that this imminent availability of additional Hib vaccine products will reduce the global vaccine price in the next few years.

One of the novel ways of making vaccines accessible and affordable to poor countries is illustrated by the Meningitis Vaccine Project (MVP), a collaboration among the WHO, the US non-profit PATH, and SIIL [92]. MVP was created in June 2001 through a grant from the Bill & Melinda Gates Foundation [92]. MVP has given funding, expertise, and technology (a push mechanism) to SIIL for the development of a monovalent meningococcal A conjugate vaccine (against group A *Neisseria meningitidis*) for use in African countries [97]. In exchange, SIIL has committed to charge a maximum price of US\$0.50 on the final product. MVP has generated a meningitis vaccine to be available by the end of 2010, which will cost no more than US \$0.50 per dose [92]. This vaccine is tailored to the needs of countries in the so-called ‘‘Meningitis Belt’’ in sub-Saharan Africa. MVP has also been urged by MSF and Oxfam to change the current

system so that donor funds incentivize the development of adapted vaccines and ensure affordable prices.

The meningococcal A (Mn A) polysaccharide (PS)–tetanus toxoid (TT) conjugate vaccine (above) was developed using reductive amination of polysaccharide aldehydes and toxoid hydrazides [23]. There are three steps involved in the preparation of the Mn A PS–TT conjugate: activation of TT, activation of Mn A PS, and conjugation of activated Mn A PS to activated TT [23]. Mn A PS is microbial based, and TT is made from broth cultures of *Clostridium tetani* (bacterial) [98]. As illustrated in Tables 1.2 and 2.1, additional savings can potentially be made in the Mn A conjugate vaccine if the components Mn A PS and TT were produced in plants.

It is well recognized that patents can increase the cost of product development, by increasing transaction costs and delaying access to research inputs, due to fragmented IP owned by multiple parties (known as anticommons) [80]. This makes investments targeting the needs of small or unprofitable markets (e.g., combating infectious diseases in developing and underdeveloped countries) difficult for private companies to justify economically, although not on moral or humanitarian grounds. Creation of anticommons in the USA has been credited to the *Bayh–Dole Act*, which established incentives for universities to develop independent technology transfer programs and manage IP in a highly individualized and even competitive framework, with respect to other universities. As outlined above (section 2.3), when IP that is developed with public funding is licensed exclusively to private companies, as has been in extensive practice since the passing of the *Bayh–Dole Act* by US Congress, the technology is typically unavailable to support product development for low income/margin markets (e.g., prophylactic vaccines). To

address this issue, a range of patenting and licensing strategies that explicitly define and reserve rights for humanitarian uses of patented technologies to allow product development for non-commercial markets have been developed [80], as discussed below.

In agriculture, publicly minded licensing is a concept illustrated by the Public Intellectual Property Resource for Agriculture (PIPRA) in response to concerns about IP impediments to research and development in subsistence crops for the developing world. The agriculture public licensing model is important to study because of its implications on PDVs, which encompasses the fields of life sciences and agriculture. In this model, a mechanism has been created by PIPRA for its members to collaboratively manage their agricultural IP with goals that focus on both individual universities' interests as well as public good. Elements from the PIPRA IP model could be applied when impediments arise in PDV access to developing and underdeveloped country markets.

Another approach to address anticommons is Biological Innovation for Open Society (BiOS), which is modeled on the open source paradigm in software. BiOS provides access to platforms of patented enabling technologies through an “open source” license that protects the BiOS technologies from private appropriation, and it builds a “commons” of IP through a grant-back provision [80]. Grant-back is a term included in a licensing agreement that provides the licensee to disclose and transfer all improvements made during the licensing period. This provision expands the initial technology pool and prevents the development of blocking patents on improvements. Publicly funded universities have also joined the effort to ensure global access to medicines/vaccines. In 2007, the University of British Columbia (UBC) adopted Global Access

License Principles in an effort to ensure that UBC's biotechnology and environmental licensees develop and market UBC-derived technologies for global benefit [99]. Under this framework, UBC has licensed a low-cost oral formulation of Amphotericin B (novel agent against leishmaniasis) to iCo Therapeutics. According to the licence agreement, iCo Therapeutics agreed to produce and sell at-cost versions of the drug (against leishmaniasis) in developing countries, in return for rights to market the drug for the treatment of blood-borne fungal infections in the developed world [99]. Elements from BIOS and the UBC Global Access License Principles IP model could be applied when impediments arise in PDV access to developing and underdeveloped country markets. The issue of access to medicines in Canada and its implications for the future of publicly funded Medicare program have been discussed in [61, 100], (with supporting evidence [102] and bulk purchase of medicine plans [101]).

3. METHODS, THEORY, AND LITERATURE REVIEW

Traditionally, life science research has been isolated, following the “standing on the shoulders of giants” model where individual efforts build upon knowledge generated by others, with little formal or informal exchange of information during the discovery phase [20]. The explosion of life science research since the 1980s and fragmented IP has resulted in increased collaboration and networking.

The literature review consists of three parts: first, a discussion about the development of models to describe the innovation process is documented. Evolution of innovation models from the simplistic linear to chain-linked networked models are illustrated with figures. Second, the economics of exchanges or transaction are discussed, drawing on both neo-classical economics and new institutional economics. Third, non-economic dimensions of networked knowledge are presented.

3.1 Innovation Process

The Merriam-Webster’s Collegiate® Dictionary, Eleventh Edition (online version) [54] defines innovation as:

- 1 : the introduction of something new, and
- 2 : a new idea, method, or device.

Many scholars have discussed the innovation process and developed its schematic representation, with two models having evolved from this. Presented below is a discussion of each of the sets of models, based on conceptual development, and not necessarily in chronological order, as relevant to the thesis. Rothwell [55] reviews the chronological evolution of innovation models:

technology push (first generation), market pull (second generation), coupling (third generation), integrated innovation (or integration and parallel development) (fourth generation), and system integration and networking (fifth generation). The push and pull models have been elaborated on in section 2.2.

3.1.1 Linear Models

Since World War II, a linear model has been used, wherein R&D leads to production and is ultimately marketed [56]. This simplistic model is shown in Figure 3.1 below. Rogers [57] represents innovation development as a linear process consisting of six stages: problem definition, research (basic and applied), development, commercialization, adoption and diffusion, and consequences.



Figure 3.1: Linear Model of Innovation (Adapted from [56]). This is one of the simplistic linear models of innovation.

Historically, the linear model of innovation positions post-secondary institutions of higher education at the earliest stage of knowledge creation and focuses on university research as the generator of ideas [58]. Feldman and Stewart [58] studied technology transfer mechanisms from academic institutions to the industry. They discussed a framework for considering the evolving role of institutions of post-secondary education in generating economic growth and development. Figure 3.2 shows both formal and informal knowledge transfer mechanisms from an academic

institution. Traditionally, emphasis has been put on formal knowledge transfers and market transactions, as these can be measured and evaluated, e.g., publication of papers, reports, patents, etc. Informal knowledge exchanges facilitate intellectual discourse leading to novel ideas, creativity, and exploration, and is within the domain of networked knowledge, as discussed in section 3.2.1. Further elaboration on types of knowledge is presented in section 3.1.3. Figure 3.3 (from [58]) represents the linear transfer of formal knowledge from academics to the industry, and identifies stages and stakeholders involved.

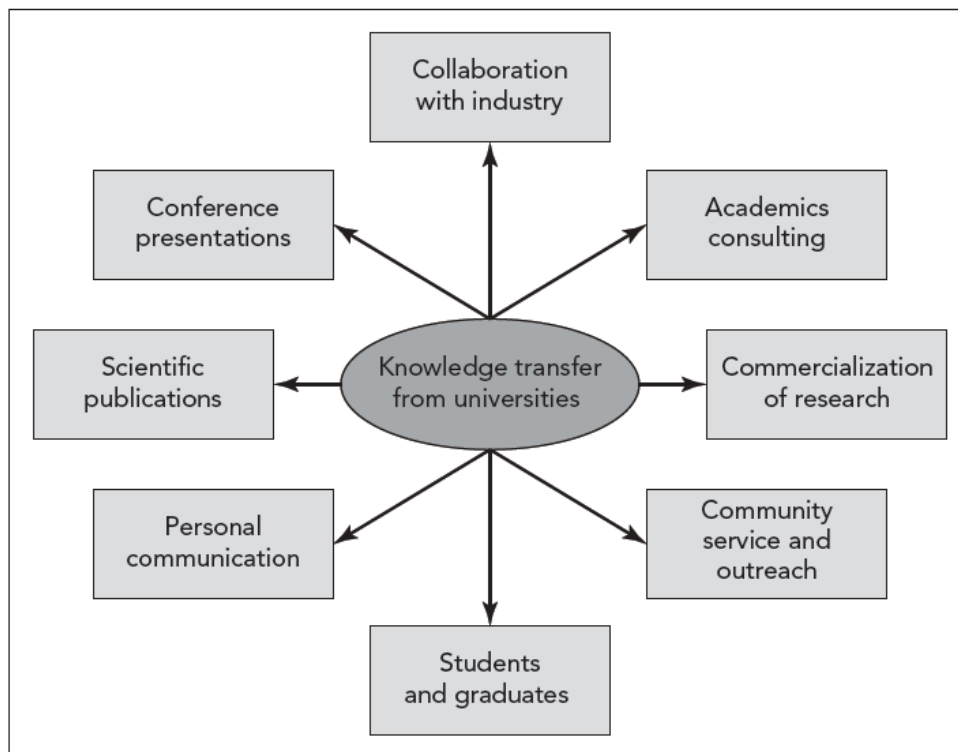


Figure 3.2: Knowledge Transfer Mechanisms from Academic Institutions (From [58]).

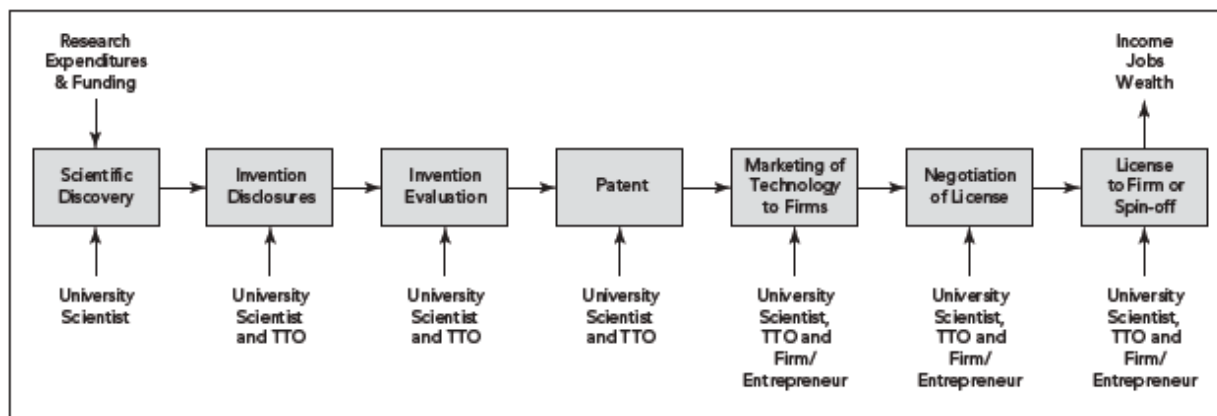


Figure 3.3: Linear Technology Transfer from Academic Institutions to Industry (From [58]).

The boxes represent knowledge flow from scientific discovery (creation), to patent protection, to licensing (transaction) and tangible benefits such as income, jobs, and wealth creation. Inputs to knowledge creation and transfer have been illustrated.

3.1.2 Non-Linear Models

Progression of an idea through an innovation process is explained to be due to two synergistic mechanisms: push and pull. Whereas a visible demand is a pull factor for the vaccine candidate in the marketplace, technical and operational feasibility is considered a push [59]. These mechanisms and their relation to vaccine innovation have been elaborated in section 2.2. The current theories on innovation, including technology push, market pull, and an organizational approach have been criticized for their lack of integration and inapplicability to the 21st century competitive environment [60].

Many success/failure studies done during the 1970s of innovation performance suggested that the coupling model (with its feedback loops and market linkages, and with the addition of limited functional overlap) more often led to success than did its linear predecessors [55]. Kline and Rosenberg [56] present their model of innovation as a non-linear, dynamic, chain-linked process to represent the relationship among the elements of research, invention, innovation, and production. Their dynamic model is illustrated in Figure 3.4a. It consists of feedback loops between each stage to the previous one, with the potential of an innovator to seek out existing knowledge, or to undertake or commission research to solve problems in the innovation process [20].

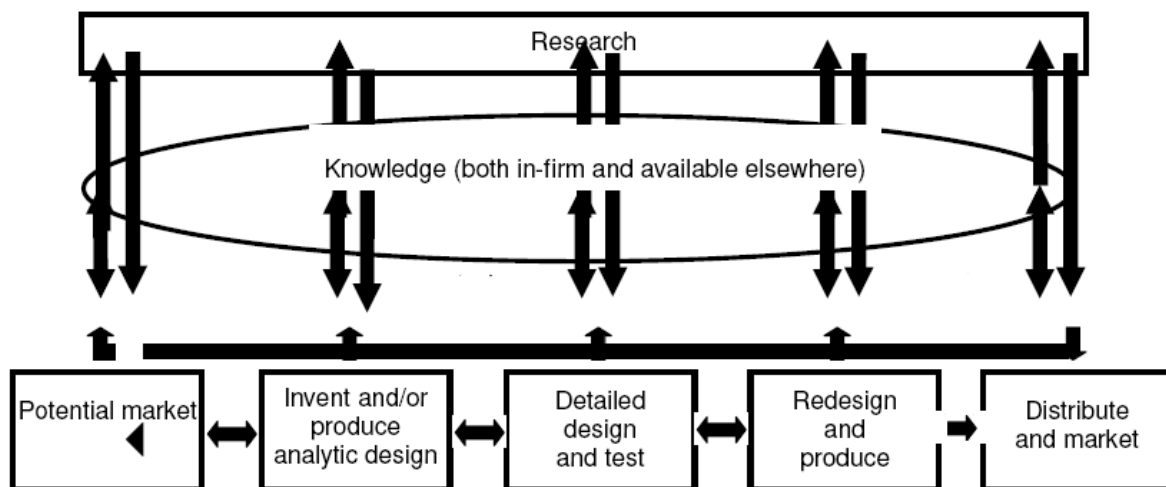


Figure 3.4a: An Adaptation of Kline and Rosenberg’s Chain-Linked Model of Innovation (From [20]). Arrows represent the flow of knowledge.

Rothwell's integrated representation of innovation can be depicted as a process of know how accumulation, or the learning process, involves elements of internal and external learning, composed of interacting and interdependent stages [55] (see Figure 3.4b). The element of internal learning involves the following processes: learning by developing; learning by testing; learning by making–production; learning by failing; learning by using in vertically integrated companies; and cross-project learning. External or joint internal/external learning involves the following: learning from/with suppliers; learning from/with lead users; learning through horizontal partnerships; learning from/with the S&T infrastructure; learning from the literature; learning from competitors' actions; learning through reverse engineering; learning from acquisitions or new personnel; learning through customer-based prototype trials; and learning through servicing/fault finding. The internal and external learning stages interact and are dependent on each other as represented by the arrows.

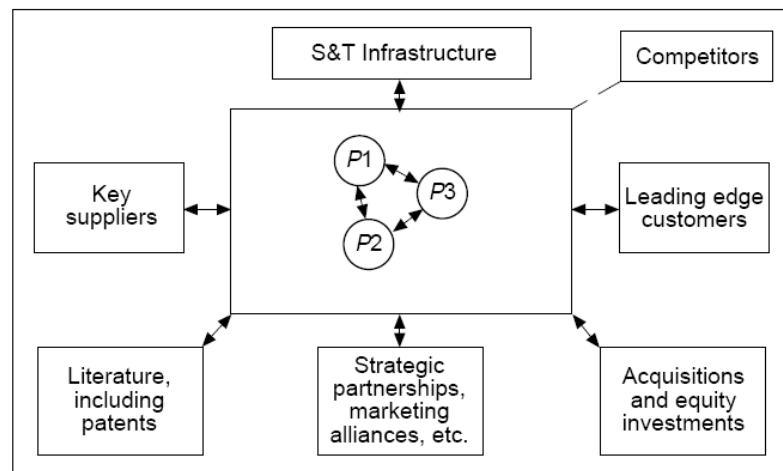


Figure 3.4b: Innovation as a Process of Know-How Accumulation (From [55]). Innovation is represented as a process of know-how accumulation, or learning process, involving elements of internal (P1, P2, etc.) and external learning, composed of interacting and interdependent stages. Arrows indicate flow of knowledge. See main text for details.

Traditionally, biotechnology innovation has been viewed in terms of sequential stages of product development over an expansive and long period. One of these later models is shown in Figure 3.5. The figure shows five different stages in product and availability: basic research, innovation and invention, early-stage technology development, product development, and production and marketing. The unique features of the model are, first, that it outlines various important activities in its life cycle, and second, that it directly refers to at least two critical functions—R&D and funding, and financing—and indirectly indicating a third one, the use of collaborations to keep companies funded and active in research [60].

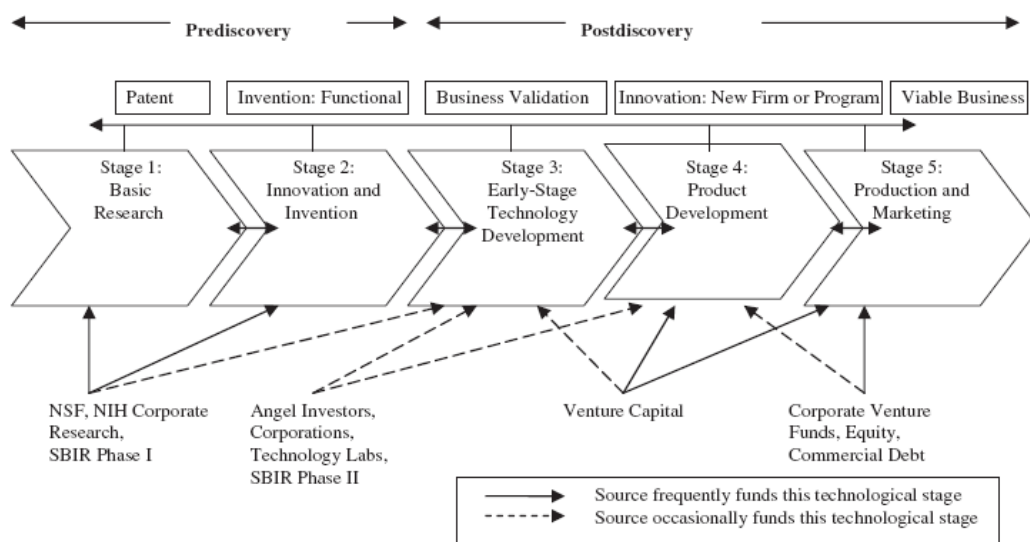


Figure 3.5: Sequential Model of Innovation (From [60]).

Khilji et al. [60] presents a sequential model of innovation (Figure 3.6), a conceptual framework for applying the integrated innovation model to biotechnology firms. They make the case for incorporating market-oriented mechanisms, building and using appropriate organizational capabilities, developing effective collaborations, and creating parallel interactions as major

elements in a general strategy toward the success and improved efficiency of biotechnology companies. This model builds on models developed with the integrated approach by previous researchers, including Rothwell [55] (as discussed in section 3.1).

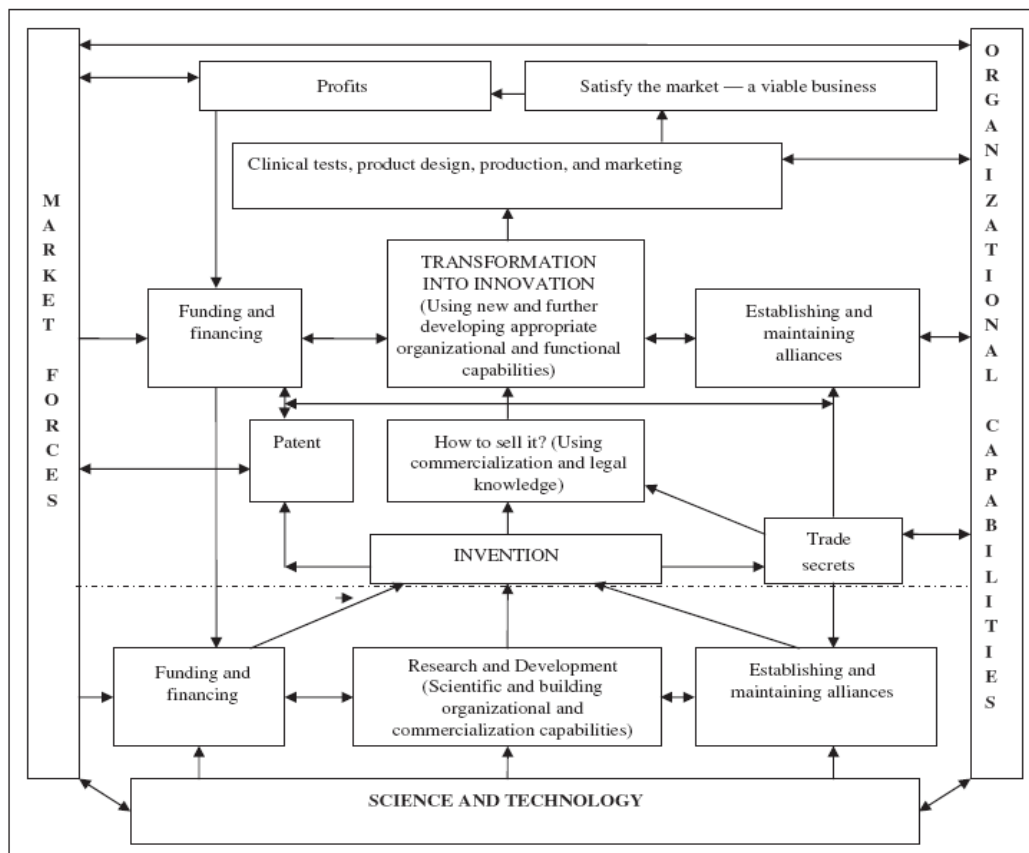


Figure 3.6: Integrated Biotechnology Innovation Model [60]. The dotted line represents the distinction between pre-invention and post-invention stages. Regulatory approvals are required both before and after clinical trials to grant or withdraw approved drug status.

3.1.3 Nature of Knowledge

Merriam-Webster's Collegiate® Dictionary, Eleventh Edition (online version) defines

knowledge as:

2 a (1) : the fact or condition of knowing something with familiarity gained through experience or association (2) : acquaintance with or understanding of a science, art, or technique b (1) : the fact or condition of being aware of something; and 4 a : the sum of what is known : the body of truth, information, and principles acquired by humankind.

In a knowledge-based economy (KBE), knowledge can be classified into four distinct kinds for the purpose of economic analysis, and have been described in detail by the OECD [62]. These are: know-why, know-what, know-how and know-who knowledge. Characteristics of the kinds of knowledge have been reviewed [20]. Whereas know-what and know-why are suggested to closely fit the marketable commodities category of knowledge with economic valuation tools, know-how and know-who forms represent the tacit form of knowledge that are more difficult to codify and measure. A detailed description of the kinds of knowledge is presented in Table 3.1 (from [20]). The understanding of knowledge types and their associated details helps to frame the analysis in phases of development in section 4.3.

Table 3.1: Classification of Types of Knowledge (From [20]).

| Knowledge Type | Degree of codification | Produced by | Extent of disclosure |
|-----------------------|-------------------------------|---|--|
| Know-why | Completely codified | Universities and public laboratories | Fully disclosed and published in scientific journals |
| Know-what | Completely codified | Universities, public laboratories and private companies | Fully disclosed in patents |
| Know-how | Not codified | Hands-on experiments in laboratories | Tacit; limited dispersion |
| Know-who | Not codified | Exists within companies or research communities | Tacit; limited to community |

3.1.4 Life Cycle of Knowledge

The “life cycle of knowledge” model developed by Alston, Norton, and Pardey [40] is central to our socio-economic analysis of PDV innovation and adoption process. The model (Figure 3.7) illustrates the time course of innovation, in terms of resource (money) inputs or benefits (revenues, represented as \$ in the amplitude). The model illustrates four distinct (but at times overlapping) phases/stages of development. A detailed explanation of the significance of the different phases and associated amplitudes is provided in section 4.3 (Chapter 4).

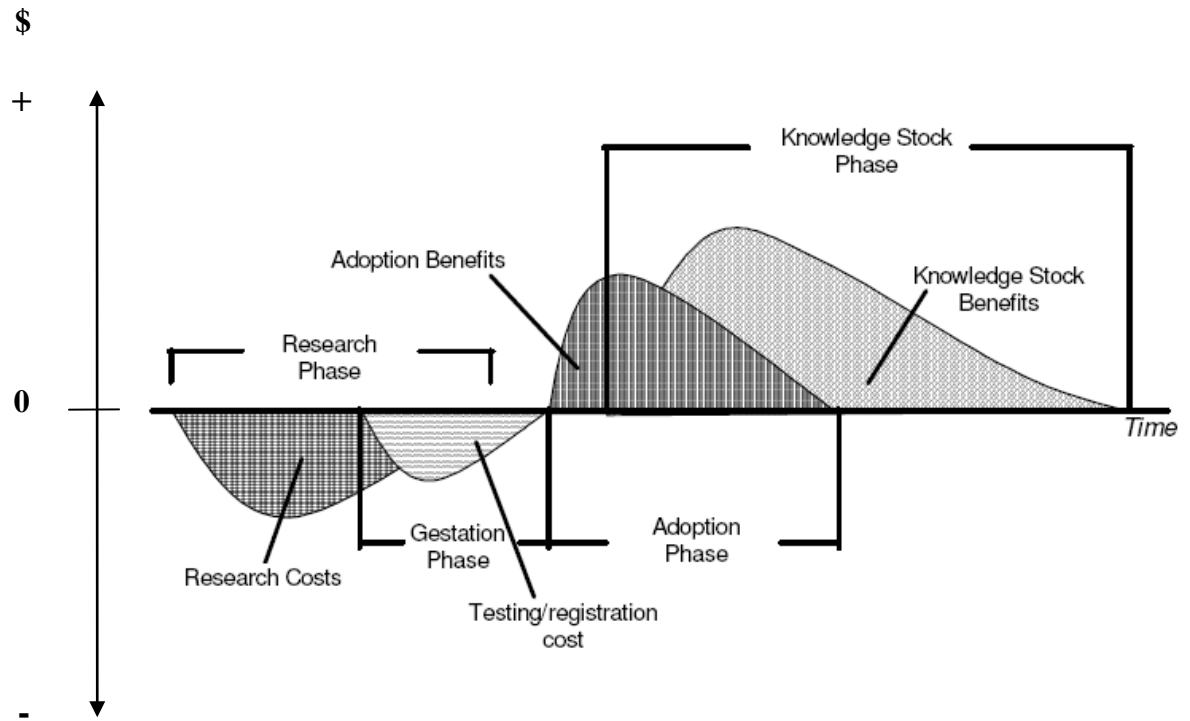


Figure 3.7: The Life Cycle of Knowledge Valuation (From [20]).

The phases of development are the following: first, the research phase that involves setting up and undertaking research; second, the gestation phase that involves proof of concept, patent and IP protection applications, and other pre-market commercialization investments; third, the adoption phase that could involve an incremental investment for IP management and product maintenance; and fourth, the knowledge stock, in which the various kinds of knowledge generated are used as inputs to further research.

3.2 Economics of Transactions

Transactions (a.k.a. deals) are common where exchange of different kinds of knowledge takes place. Transaction cost theories applicable to innovation processes have been reviewed [20, 63]. It is suggested that the control variable of analysis is the transaction, and that the two approaches to mitigate the potential cost of opportunistic behaviour in a buyer–seller relationship (e.g., between a research-intensive and a manufacturing company) are contractual relationships and vertical integration. According to transaction cost economics, the ultimate objective for both parties in a relationship is to minimize transaction costs [49]. Partnership is suggested to be one of the mechanisms to reach that objective, as detailed in section 3.3 and illustrated with a business case study in 4.3.1 subsection Transactional Forms and Institutional Structures > Characteristics.

3.2.1 Economic Definition of a Transaction

A transaction is said to occur when a good or service is transferred across a technologically separable interface [20], e.g., when a research institution licenses their invention to a manufacturing/marketing company for manufacture and distribution. Nobel laureate economist Amartya Sen argues that the standard economic models put a lot of focus on exchange, mainly of commodities, as opposed to exchange of speech, claims, proposals, and settlement [64].

Transactions can be characterized by their structure and dimensions, and involve three cost components, relating to search, negotiation, and enforcement. For example, the research institute and manufacturing company (above) would incur costs for searching, negotiating, and enforcing the license, although different amounts for either parties. Three principal dimensions in which

transactions may differ from one another, with respect to their relative costs are the following: first, transaction uncertainty may vary, depending on the extent of communication or strategic behaviour; second, the frequency of a transaction, i.e., occasional or recurring, can influence costs; and third, asset specificity arises when the opportunity cost of a particular transaction is much lower in its best alternative use; thus, when the original transaction is terminated, the asset has reduced value.

Agency theory provides a complementary explanation for the transaction costs [20]. The theory assumes that firms (“principals”) contract with “agents” to avoid market risk inherent in arms-length market transactions. An agency dilemma occurs when a principal is unable to adequately monitor or assess an agent’s behaviour, i.e., when the agent’s task is less programmable, when accomplishing the task entails risks, or when the goals of the principal and agent are in conflict [65]. Task programmability is the contribution of inputs by the agents to the task. Non-separability is the contribution to the total output. These terms will be used frequently in the analysis later.

Mahoney [41] provides a synthesis of agency theory and asset specificity to explain the various institutional structures and agreements that might emerge to manage different types of transactions, as described in Table 3.2. These transactions cover a spectrum from simple, arms-length spot markets to fully vertically integrated operations, with a number of non-market relationships (e.g., hierarchy, clan, or cluster communities with established norms) to deal with network-generated knowledge.

Table 3.2: Transaction Forms in Different Situations (adapted from [20]).

| Situations | Low Task Programmability | | High Task Programmability | |
|------------------------------|---------------------------------|------------------------|----------------------------------|------------------------|
| | Low asset-specificity | High asset-specificity | Low asset-specificity | High asset-specificity |
| Low Non-Separability | Spot market | Long-term contract | Spot market | Joint venture |
| High Non-Separability | Relational contract | Clan (hierarchy) | Inside contract | Hierarchy |

3.2.2 Institutional Structures

Discussion of the institutional structures that govern the generation and use of knowledge is integral to the analysis of introduction and adoption of new biotechnology products. There are three main kinds of institutional structures [20] that participate in the innovation process and deliver marketable products and/or services: public, market (private), and the voluntary sectors. The kinds of pure goods delivered by these institutions are public, market, and common pool goods. These structures are represented in the Picciotto model in Figure 1.4.

In Figure 1.4, the public or state sector A represents the citizens of a country and pursues policies to maximize the interests of society altogether, producing public goods; the market sector C owns property and attempts to maximize profits on those investments by producing private market goods; and the voluntary sector/civil society groups E consists of those that join a project to reap the benefits of collective action and to pursue goals that cannot otherwise be accomplished through individual action (e.g., common pool goods). The public sector is optimally suited for creating public good and know-why scientific knowledge, and uses a social

welfare evaluation framework for decision making. In contrast, private firms use valuation models derived from accountancy to optimize the net present value of investments in technology development. Collective organizations are ideally suited to deliver know-how and know-who knowledge.

In Figure 1.4, the intersecting areas labelled B, D, F, and G represent institutions that operate between and within the overlapping dominant areas of the public, market, and voluntary sectors (public organizations, NGOs, and hybrid corporations, respectively) and are suggested to be a domain of networked knowledge [20]. These overlapping institutions have been reviewed in detail [21]. The overlap between government and private goods B are considered to be toll goods, within the scope of public (e.g., SaskWater—water and waste water services in the province of Saskatchewan) or regulated private corporations and can be in the form of public utilities. The overlap between private and common pool goods D are civil goods. Institutions in this category are NGOs, e.g., public advocacy/interest groups, professional standards, and civic action. The overlap between common pool and government goods F are public goods. This domain consists of hybrid organizations that are responsible for issues like rural roads. The original Picciotto model fails to explain the profile of institutional structures operating in the center of the framework where all the spheres overlap G [21]. Smyth [21] provides an insight into potential importance and constitution of this area from a regulatory governance perspective. It is suggested [21] that G is of great importance to PDVs (and plant-made pharmaceuticals collectively) as a third generation plant biotechnology product, where there is a regulatory vacuum due to much advanced science currently compared to established regulation. The regulatory pathway is still not clear and the federal government is investigating policy options

for commercial production of PDVs [66]. Public institutions involved in regulatory oversight of PDVs consist of CFIA and Health Canada (see section 2.2.2 subsection Regulatory). It is argued that the regulatory management of PDVs in the area G could be a shared function effectively done by government regulatory agencies, the private industry associations, and the judicial system.

Areas A and C in Figure 1.4 would represent the operations of federal government agencies (such as the CFIA) and the biotechnology industry (e.g., BIOTECCanada), respectively, for regulation of novel biotechnology products. In the case of a dispute between A and C, the area of overlap is under the jurisdiction of civil courts. However, most cases referred to the Supreme Court of Canada is on social policy, over which the court does not have jurisdiction [21]. This situation is within the scope of the Auditor General of Canada. The structure of interaction of CFIA and the biotechnology industry in Canada does not allow public participation. The interaction between A and E is usually in the form of Royal Commissions, specially structured government committees and government organized public forums, e.g., Canadian Biotechnology Advisory Committee (CBAC). The interaction of C and E is twofold: first, through civil courts in the case that the public, as consumers, is not satisfied with industry-established quality assurance policies (illustrated with biotechnology business cases in section 1.2.3). Second, the emerging role of media in assuming the role of industry watchdog has been emphasized [21]. Both mainstream media and new media cooperatives, in online and print format, can assume this role. One example of new media cooperative in Canada would be the Media Co-op. The Media Co-op is a network of member-supported, local democratic news organizations across Canada that

has been publishing since May 2003 [<http://www.mediacoop.ca/info/about>] The Media Co-op publishes the Dominion, with locals in Halifax, Vancouver, Montreal, and Toronto.

3.3 Hypothesis: Partnerships as Enabling Mechanism

Innovation in life sciences has been argued to resemble a non-linear, chain-linked “networked” structure [20], as also discussed in section 3.1.2. In the Canadian context, most networked research has been precipitated and partially supported by government departments and agencies [20]. Some examples are the Genome Canada program partially supported by Industry Canada, and the Networks of Centers of Excellence (NCE) program administered by the Research Councils (NSERC, SSHRC and CIHR) in partnership with Industry Canada. Phillips and Khachatourians have presented a detailed study of one such networked structure involved in the transformation of the canola industry by biotechnology [67]. The Abiotic Stress Project, a Genome Canada project, has been analyzed within the framework of innovation models, transaction economics, and networking mechanisms [20].

The primary objective of the thesis is to explore whether SME partnership would be a good business model for the introduction and adoption of PDVs. It is hypothesized that SME partnership as a business model might work for introduction and adoption of PDVs. In the kind of business model under investigation, a research-intensive privately or publicly traded biotechnology SME usually forms PPP in research networks and strategic partnerships with large pharmaceutical/biotechnology companies for manufacture and/or distribution. The hypothesis is tested in Chapter 4.

Trends indicate that research-oriented biotechnology SMEs have emerged as significant players in the development of new vaccine and biopharmaceutical candidates [63]. This trend continues as traditional large-scale in-house research in large pharmaceutical companies is no longer the predominant mode in the industry [63]. Research programs (see section 4.3) in biotechnology SMEs tend to exhibit high non-separability; i.e., it is difficult to determine the output of an individual. Literature therefore suggests monitoring output is one of the most important features of R&D intensive biotechnology SMEs. Subsequently, it is important to develop a good mechanism to adequately reward hard and productive work [63].

The final product of SME biotechnology companies is usually the creation of scientific innovation [63], which serves as input for large pharmaceutical companies that produce and market the final product (e.g., vaccines) to customers [63]. These entities (biotechnology SMEs and large pharmaceutical companies) have a buyer–seller relationship. To mitigate the potential cost of opportunistic behaviour between the entities, either a contractual (collaborative) relationship or vertical integration might be a good fit [63]. Patent hold-up is reported to be a challenge in the highly R&D-intensive biotechnology industry [63]. Because monitoring is critical, vertical integration may not be a desirable solution to hold-up problems [63]. Thus, according to transaction cost theory, a feasible alternative is to form strategic alliances (partnerships) [63].

A key hypothesis of transaction cost economics (section 3.2) is that partners choose a governance structure that minimizes transaction costs [49]. This means transaction costs could be reduced by choosing appropriate partners and governance structures. It is shown later in 4.3.1

(subsection Transactional Forms and Institutional Structures > Characteristics) how a PDV SME reduced transaction costs by choosing appropriate partners and governance structures.

Pros and cons of partnership in achieving organizational objectives for private companies have been reviewed [68]. It has been suggested that the complexity of a joint project, difficulties in relinquishing control, and a lack of trust between the parties are barriers to a successful collaboration [63]. It is also suggested that successful partnerships view their relationship not as a transaction between two companies, but as a transformation that enables them to work together in an entirely new mode [68]. The thesis indicates that some objectives that SME biotechnology companies strive for (and that give them a competitive advantage) occur by partnering with other SMEs and/or large companies. Among these objectives are access to product pipeline and/or IP; R&D [63]; access to distribution network; access to production facilities; access to financial resources (alliance capital) [63]; and expanding markets. For a detailed discussion on examples of these objectives, see section 4.2.

It has been indicated that partnerships and strategic alliances have a strong effect on success of SME life science businesses. Researchers with Deloitte Services/Deloitte Consulting/Deloitte & Touche surveying the biotechnology industry found that, although the importance of partnering has long been recognized, developing and maintaining effective cross-sector partnerships is not yet common practice [68]. Small life science companies, for example in Vancouver, B.C., have become very successful through strategic partnerships with major international firms [69].

4. ANALYSIS AND MODELLING

4.1 Introduction

This chapter presents analysis of two separate business case studies, each of which are attempting to commercialize a PDV. The analyses will illustrate each phase of development within the theoretical framework discussed in Chapter 3. In sections that follow, the generation and use of knowledge, the agreements secured to administer, and the institutional structures that facilitate each phase are presented from the two studied business case studies.

4.2 Analysis of Two Business Case Studies

Two institutional situations are illustrated and analyzed:

- Business case study A: A publicly traded biotechnology company, Medicago Inc., based in Eastern Canada that is commercializing PDVs (see Table 4.1); and
- Business case study B: An academic institution based in the USA collaborating with an American agricultural biotechnology Dow AgroSciences limited liability company (LLC) to commercialize PDVs (see Table 4.1). Dow AgroSciences is a wholly owned subsidiary of a publicly traded corporation, The Dow Chemical Company.

The literature indicates that most biotechnology companies strategically work to develop a PDV platform technology and vaccine candidates/products that are just spinoffs from these platform technologies. This argument is further supported by Andrew Sheldon's (CEO, Medicago) interview with the *Globe and Mail* in 2008: "If the influenza vaccine proves successful, Medicago intends to apply the tobacco-harvesting technology to make vaccines for everything

from malaria to HIV” [70]. Oftentimes, the choice of these vaccine candidates are market driven, e.g., Medicargo’s influenza vaccine candidates. The companies place special value on these platform technologies (usually IP protected as a suite/family of patents) as their IP assets, which they use as a tool to raise public and/or private capital of different forms (venture capital, IPO, etc.). Drawing on the discussion of economics of transaction from section 3.2 (Chapter 3), it was highlighted that transactions are common where exchange of different kinds of knowledge takes place. It is relevant to note that transactions occur when capital is raised by a company, as there are knowledge exchanges between the company and the community of investors.

4.2.1 Business Case Study A

The priority IP was developed by collaboration between Agriculture and Agri-Food Canada, Sainte-Foy (in Québec City, Québec), a Canadian federal government department (public lab), the Canadian Red Cross Society (a non-profit, humanitarian organization), and Université Laval (a public university located in Québec City). The IP was subsequently licensed to Medicargo Inc., a company that was founded in 1997 [71] and incorporated in 1999. Since establishment, Medicargo has received significant public investment. This public investment includes funding from National Research Council IRAP [<http://www.nrc-cnrc.gc.ca/eng/news/nrc/2010/08/25/medicargo-irap.html>] and CIHR [<http://www.medicargo.com/English/news/News-Releases/News-ReleaseDetails/2010/300000CanadianInstitutesofHealthResearchgrantawardedtoMedicargoMcGillUniversityandtheResearchInstituteoftheMcGillUniversityHea/default.aspx>] for basic immunological research and product development. Medicargo went public in 2006 and is being traded on the Toronto Stock Exchange.

Initially, Medicago focused on genetically engineered alfalfa (*Medicago sativa* L.) lines to produce recombinant proteins for human, veterinary, and industrial applications [71]. Proficia™ is Medicago's platform technology. In 2006, Medicago made a dramatic shift in business emphasis by focusing on the influenza vaccine market, and for this purpose, switching from alfalfa plants (to generate drugs and proteins) to tobacco as the manufacturing medium [70]. The latter platform scores better in production speed (four weeks) compared to alfalfa (eight months), which is crucial for developing seasonal and pandemic influenza vaccine production. This change in business emphasis was purely a result of projected market pull due to an increasing fear of influenza pandemic in 2006, and boosted by rising government funding into influenza vaccine research. Indication of national pandemic preparedness plans positively influencing business growths in vaccine development found in this thesis has also been documented by authors in the past [72].

Dr. Louis-Philippe Vézina and François Arcand co-founded Medicago. Dr. Vézina obtained his Ph.D. in plant biochemistry at Université Laval and worked as a research scientist in the GE group of a large alfalfa project at Soils and Crops Research and Development Centre (AAFC) in Sainte-Foy [71]. Mr. Arcand was former CEO (1997–2002) of Medicago and is the current CEO of ERA Biotech [73]. He has an executive MBA from John Molson School of Business, Concordia University, Montréal.

The competitive advantages of Medicago are, first, manufacturing advantages of transient expression in plants (speed and cost), and second, the VLP advantage as an antigen (breadth of the immune reaction, cross-reactivity, and one-dose product) [74]. Currently, the market supply for inactivated seasonal influenza vaccines is produced twice yearly in embryonated chicken eggs. It takes six months after the identification of influenza strains by WHO international surveillance system to begin production [18]. In April 2009, Novavax, a small biopharmaceutical company located in Rockville, MD, produced a VLP vaccine candidate for the H1N1 strain [9] in insect cell culture and recombinant baculovirus cultures [19]. Medicago successfully expressed a H1 VLP antigen, a vaccine candidate against the new strain of influenza A (H1N1), within 14 days of receiving the genetic sequence of the new virus [75], much faster than expression in embryonated chicken eggs, and insect cell- or recombinant-baculovirus culture.

Compared to other vaccine production platforms, egg-based manufacturing systems suffer from limited capacity, poor flexibility, and restricted responsiveness, decreasing the effectiveness of this system in a pandemic [17]. It is thus clear why alternative systems (e.g., PDVs) to complement supply are contemplated.

4.2.2 Business Case Study B

The idea to invent oral immunization by transgenic plants has been reviewed in section 2.1.1. The project to develop a plant-based gene expression technology to produce antigens for vaccines was a collaborative effort of researchers involving Drs. Cardineau and Curtiss, from Biodesign Institute at ASU working with Dow AgroSciences.

In 2005, a news release¹ indicated this group entered a formal two-year research and collaboration agreement (transaction as discussed in section 3.2) to bring forward plant-made technology advancements to create plant-made vaccines for the animal health industry.

Later, in 2006, a Newcastle disease virus (NDV) vaccine developed at Animal Health Unit of Dow AgroSciences by this collaboration and others was the world's first PDV to get approved for commercial sale [44]. Dow AgroSciences does not plan to commercialize the NDV vaccine product. As NDV is well known and understood by the regulatory agency (USDA) it served as an excellent model to prove Dow AgroSciences' new plant based vaccine production technology. A 2006 Dow AgroSciences news release indicates that in fewer than five years, the company moved the science forward, established a production facility, and received this regulatory approval milestone [44]. Careful evaluation leads to interpreting this "moving the science forward" as a development since the beginning of ASU PDV platform research project, which is estimated to be around 2001. This estimate suggests that Dow AgroSciences had established some informal know-how and know-who knowledge exchange(s) with Biodesign Institute at ASU since at least 2001.

¹Dow AgroSciences, Biodesign Institute at Arizona State University Collaborate in Advancing Plant-Made Vaccine Platform. 2005 [cited 12 May 2010]; Available from: <http://www.dowagro.com/animalhealth/resources/news/20060131b.htm>.

Business case study B in this analysis specifically refers to the PDV project at Dow Agro Sciences/Biodesign Institute at ASU. Concert™ Plant-Cell-Produced System is their platform technology. This business case study will be presented in this thesis whenever required to complement the prerequisite analysis with a US perspective.

The plant-cell-produced vaccine production system developed by Dow AgroSciences is based on the use of a recombinant plant cell line, which could be a potato, tomato or tobacco plant cell. Dow AgroSciences is actively working on a pipeline of plant cell-based vaccine candidate products which are all at different stages of commercialization with final products anticipated within a decade.

The general process development strategy followed by Dow AgroSciences has been documented¹ and is described below. There are several sequential steps involved. First, the plant cells are transformed using conventional plant cell biology techniques to introduce the desired antigen. Second, a master seed is established and vaccine antigen is prepared by growing the cells in a conventional bioreactor. The plant cells are then grown in a defined culture medium comprised primarily of water, a carbohydrate source, minerals and salts. The cells are harvested

¹Mihaliak, C.A. and S.R. Webb. Plant-Cell-Produced Vaccine for Animal Health. 2005 [cited 6 September 2011]; Available from:

http://www.dowagro.com/PublishedLiterature/dh_004d/0901b8038004d659.pdf?filepath=/PublishToInternet/InternetDOWAGRO/animalhealth/pdfs/noreg/010-99016&fromPage=BasicSearch

and processed once sufficient replication occurs. Formulation is then done for the bulk antigen for delivery. Current process development involves this basic process followed for four different antigens. This strategy indicates the potential for a universal production system in which multiple antigens can be expressed and delivered using a single production system.

In order to determine the feasibility of the plant-cell produced production system for delivering vaccines to the poultry and livestock industries a series of studies have been conducted. Three requirements have been established to demonstrate proof of concept of the vaccine. First, is a demonstration that the plant cells can successfully express the antigen. Second, the antigens must induce immunity when delivered to the target species. Finally, the vaccinated animals must be protected when challenged with disease. All three proof-of-concept criteria have been demonstrated in vaccinations and challenge studies in birds.

Dow's objective in getting this NDV approval was to demonstrate that the Concert Plant-Cell-Produced system is capable of producing a vaccine that is safe and effective and to demonstrate that it meets the requirements for approval under the rigorous USDA regulatory system.

Moving forward, research will examine immunity to various virus strains and additional disease targets in addition to exploring mass delivery capabilities. To further develop, test and commercially validate the technology continued development will require leveraging the expertise of academic specialists, poultry and livestock industry experts. In that direction, Dow AgroSciences has worked closely with the Boyce Thompson Institute for Plant Research, Arizona State University, Benchmark Biolabs and the U.S. Department of Agriculture.

Concert Plant-Cell-Produced¹ vaccines eliminate the environmental concerns associated with other plant-based methods because the system uses only plant cells — not the whole plant – to produce vaccines. The plant cells are grown in a culture medium comprised primarily of sugar, salt and water. Concerns about transfer of seed, pollen or plant parts into the environment is eliminated because no seeds are planted, no whole plants are grown, and no pollen being produced. Plant-cell-produced vaccines are grown in stainless steel tanks by Dow AgroSciences in a bio-contained facility. Additionally, these cells are non-propagative, i.e. they cannot grow outside the culture medium.

Table 4.1 outlines a comparison of business case studies A and B in terms of parameters such as company size, IP, platform technology, market, location, etc.

¹An Ounce of Prevention. [cited 13 September 2011]; Available from: http://www.dow.com/news/feature/2006/05_22_06/.

Table 4.1: Details of Business Case Study Profiles*.

| Parameter | Case Study A | Case Study B |
|--|-------------------------------|-------------------------------------|
| Size ** | Small | Large |
| IP | Own | Owned in fragments |
| Platform technology | Proficia™ | Concert™ Plant-Cell-Produced System |
| Platform | Whole living plants (tobacco) | Plant cell culture |
| Stage (Year) of development † | Gestation phase (1999) | Gestation phase (2001§) |
| Market | Identified | Identified |
| Location | Canada (East) | United States |
| Funding/Investment | Public & private | Public & private |
| Ownership | Publicly traded | Private |
| Manufacturing Capability | Under construction (2010) | Yes [7] |
| Collaboration with Companies/Institutions | Yes | Yes |

* Business case study A = Medicago Inc., Business case study B = ASU/Dow AgroSciences LLC.

** Definition according to Industry Canada [77]; for goods producer companies, micro is 1-4 employees, small is 5-99 employees, medium is 100-499 employees and large is 500 + employees.

† Analysis of knowledge/technology life cycle, see section Phases of Development. Year here refers to the year when the PDV project started.

§ Estimated year, see section 4.2.2.

4.3 Phases of Development

Knowledge generation and use can be represented as phases of development over a time period.

Comparing Alston, Norton, and Pardey's original model [40], Peter Phillips's adaption of Alston,

Norton, and Pardey's model [20], and the time scale illustration by Khilji et al. [60] provides us

an estimate of time period for each of the few phases, research (requires around 6.5 years), gestation (around 8.5 years), adoption (around 6 years), and knowledge stock (around 9 years).

The estimation of phases of development over time is based purely on agricultural biotechnology product/knowledge life cycle [20, 40]. The thesis explores phases of development of a transformative innovation (PDVs) that is both in the domain of agricultural biotechnology and biopharmaceutical product/knowledge development. It is thus argued that there might be a margin of error for projecting a PDV product/knowledge life cycle based on only agricultural biotechnology–focused product/knowledge life cycle.

Drawing on the discussion from section 3.1.4, it was shown that Figure 3.7 represents the life cycle of knowledge valuation, with money represented as the amplitude and time as X-axis. Dollars spent is represented as the negative amplitude, and dollars earned as positive. There are costs incurred and investments made during research (research costs), and gestation phases (testing/registration costs); and benefits accumulated/used during adoption (adoption benefits) and knowledge stock phases (knowledge stock benefits).

Different stakeholders (actors) in the innovation spectrum have interest in particular interpretations of the phases of development [20]. Private or collective actors tend to ignore some or all of the costs (e.g., public goods provided as inputs to the research phase) or benefits (e.g., the knowledge stock phase, as discussed in section knowledge phase). Each of the actors is assumed to be attempting to optimize their risk-adjusted net present value of their benefits, net of their costs.

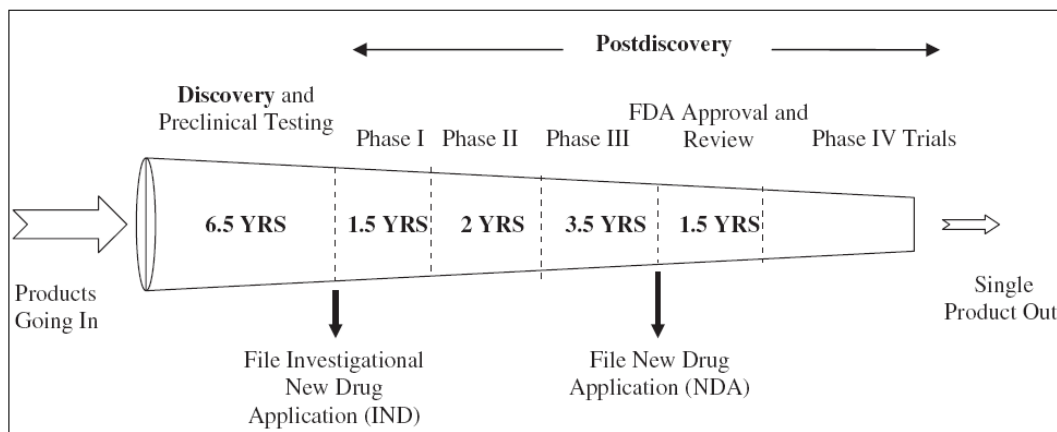


Figure 4.1: Biopharmaceutical Product Life Cycle [60].

Considering the analysis discussed in the beginning of this section, both Medicago's Proficia™ technology and Dow AgroSciences' Concert™ Plant-Cell-Produced System are currently in the gestation phase (see also Table 4.1).

4.3.1 Research Phase

Advancements in immunology, microbiology, genomics, and related scientific and technical knowledge since the 1990s have generated an explosion in vaccine R&D activities. This explosion has been fuelled by increased focus and investment in vaccine candidate pipelines by private companies. Focus has shifted away from vaccines being a low-profit, high-risk biological product especially in light of big pharmaceutical companies losing profits to competition from generic products, drying product pipelines, increased regulation and costs [9, 78]. These advancements have added several layers to the already complex and fragmented

vaccine/biological product research process, as has been documented by the proliferation of fragmented IP protection (discussed below in 4.3.1 subsection IP Protection) and increased ownership of scientific inventions.

The primary challenge of any research project is identified to be developing and initiating it in the first place [20]. This task involves finding the appropriate teams to do the work (embodying the know-how and know-who) and acquiring the appropriate rights to prior art (either public domain knowledge, or by negotiating research and commercialization licenses to patented technologies). Subsequently, the main costs involved in this phase are research costs, represented as the negative amplitude in Figure 4.1. A break-up of that would be costs involved in assembling a team with appropriate research expertise, negotiating research contracts, negotiating appropriate rights to prior art, etc. This subsection discusses some aspects of the research phase namely, IP protection, developed nation focused product, cooperation and networking, and transactional forms and institutional structures.

Intellectual Property Protection: Ideally, IP protection of novel invention serves the purpose of providing a financial incentive to the inventor(s) for potential commercial development of the invention (or idea) to benefit the society. For example, granting a patent legally excludes anybody and everybody from making, using, selling, offering for sale, or importing the developed idea and /or product for a period of 20 years (in the USA), other than the inventor(s) and/or their assignees (usually sponsors and/or employers). In the USA, there has been an almost-tenfold increase in university involvement in the patenting and licensing of inventions since the *Bayh–Dole Act* (1980) [79]. This Act allowed institutions to own inventions resulting

from federally sponsored research and to exclusively license those inventions [80]. PDV innovation fits within many existing IP regimes and it is therefore difficult to categorize PDVs for the purpose of IP protection; it is a plant variety, a drug, a biotechnological innovation, and a developing nation-focused public health tool, all in one [81].

Developing Nation-Focused Product: The characteristics of PDVs that have made them very attractive for use as prophylactics in developing and underdeveloped countries are cost effectiveness and safety, and transferable and highly scalable technology. On the other hand, access and affordability hinder the application of many currently available medicines in developing nation environments [81]. Ways to make PDVs accessible and affordable in developing and underdeveloped countries is outlined in section 2.3.

Cooperation and Networking: Life science and vaccine research is inherently tacit, making it increasingly complex and IP ownership fragmented. Researchers therefore have to constantly access third party IP and know-how knowledge to start and continue with own research programs (discussed in section 3.0 and illustrated in 4.3.1 subsection Transactional Forms and Institutional Structures > Characteristics, below). In order to decrease the transaction costs, collaborating and partnering, fostering both formal and informal relationships across the research and licensing community, have therefore increased, as shown in section 4.3.1.

It is common knowledge that the private sector is profit driven, and it exists to make a competitive return on investment. Because the market for the poor countries (low- and medium-income/LMI) does not provide this return, the private sector is not interested in investing in

developing vaccines for the developing and under developed countries. In recent years, governments and private philanthropic foundations have stepped in by funding PDV research initiatives to address the widely acknowledged imbalance of a lack of investment in R&D for health technologies for the poor [15]. This is primarily achieved through public–private partnerships (PPP).

Previous research has identified potential advantages and disadvantages of partnership during the research phase [68]. Potential advantages include sharing of risk, speed and cost advantages over other research approaches, sharing of regulatory expertise, and facilities. Potential disadvantages include absence of compatible partners, and challenges in sharing proprietary control and managing IP.

Table 4.2: Implications of Strategic Goals and Technical Factors in the Research Phase (From [20]).

| Factor | Implications |
|--------------------------|--|
| Strategic Goal | <ul style="list-style-type: none"> • Search for, and negotiation of, a research project • Assembling codified, know why and know what knowledge • Combining this with tacit know-how and know-who • Creation of a new product or process |
| Technical Factors | <ul style="list-style-type: none"> • One time transactions, involving low task-programmability, low non-separability and high asset-specificity |

Using the theoretical framework outlined in Chapter 3, the types of knowledge generated and used, and the institutions needed to handle the transactions and relationships can be identified. Table 4.2 shows the implications of strategic goals and technical factors in the research phase.

The informal and formal knowledge exchanges and transactions occurring during the research phase will also be discussed with illustrative examples relating to the business case studies.

Transactional Forms and Institutional Structures: This subsection analyzes the research agreements and institutional structures prevalent in research phase.

Research Agreements: Option agreements are common agreements in the research phase.

In this type of agreement, the licensee gets a patented technology (or multiple) from the licensor, for further R&D or other non-commercial purposes, for an option period or term (mostly 8–12 months), for specified amount of money (option fee). The option term is followed by a negotiation period where the licensee has an option to negotiate a commercial license agreement to this technology. The execution of a license would allow the licensee to legally utilize the licensed technology for commercial purposes for the duration of the license (in years) and the licensor receives timely payment of licensee fee.

In business case study A, between 1999 and 2001, Dr. Vézina had negotiated a license from AAFC [71], where the knowledge for protein production in transformed alfalfa technology was developed (see also US Patent 5,990,385 [103]). This technology was later refined at Medicago independent of host plant species to be called Proficia™ platform technology. Medicago opened its R&D laboratories and greenhouses in 1999 [71]. In 2000, it formed a Strategic Development Team to begin selling the rights to this technology. In 2001, it implemented its Prototype Development Unit to service the first commercial agreements, and continued doing so in its Dedicated Production Units in 2002.

At the same time frame, BTG International, Inc. had sublicensed a pollen electro-transformation technology to Medicago in June 1999 [104]. This technology was developed around in 1992 by Agricultural Research Services (ARS) of the United States Department of Agriculture (USDA) and patent protected as a result of research agreements with BTG International. ARS and BTG scientists worked together to put the technology into practice for tobacco, corn, and alfalfa plants. BTG International had in-licensed the pollen electro-transformation technology in 1993 from ARS. It is understood that the electro-transformation technology served as an enabling technology for Medicago to create recombinant varieties of perennial forage legumes such as alfalfa and clover to produce pharmaceutical proteins and antibodies.

The history above illustrates that IP/technology developed by AAFC, USDA-ARS, and others served as background knowledge/prior art to which Medicago had to gain access prior to starting its research phase. It has been said that in this complex age of life science research, no single company has full freedom to operate without negotiating access to someone else's technology [20]. The formal research and license agreements discussed above constitute transactions as explained in section 3.2, and their characteristics are discussed below.

Characteristics: Today, the public sector through PPP is making substantially increased investments in health technology innovation [15]. In the past, these institutional structures faced a common problem of how to manage IP. In this thesis, the framework offered by

Mahoney [41] issued to determine the optimal, actual and options or choices of institutional structure(s) that can handle the exchange of the factors that influence generation and use of knowledge. These are shown in Table 4.3.

Structuring and managing research projects are becoming very time consuming due to the need for both, an extensive search for the right partners and input, and the negotiation of the terms of exchange and common action. Full and long-term contracts would be optimal economically where full information is available and where there are no transaction costs. However, it is observed that transaction costs are premium (non-zero and high value) and the probability of having commercial success in any given project is relatively low. In present, usually less than 10% of projects return the costs of the investment. As a result, it is somewhere less likely that a full contract will be developed between the parties [20].

The research programs presented earlier tend to exhibit low task-programmability (i.e., partners cannot be told how to engage in discovery activities), high non-separability (i.e., it is hard to determine output of an individual) and the results have very high asset-specificity (i.e., the technology or product often has a very specific use).

According to Mahoney's framework, this situation of low-task programmability and high asset-specificity, with high non-separability (as above) represents a worst-case scenario in which input and output measurements of research are ineffective [41]. This situation is a perfect trigger for a "financing gap," a term also called "Death Valley" by economists/technology-transfer professionals, where investors are reluctant to invest

because they are unable to measure the output of research and associated value of their investment. This financing gap is represented as pre-commercial gap in Figure 4.2 (taken from Sustainable Development Technology Canada's (SDTC) portfolio website [http://www.sdtc.ca/index.php?page=about-our-funds&hl=en_CA]). Mahoney [41] suggests a viable solution (also see Table 3.2) to address this difficult economic dilemma is forging a clan or hierarchical relationships, where opportunistic attitudes are transformed in favour of human solidarity. In the modern sense of the word, a clan would be exemplified as a research cluster, e.g., the Saskatoon agricultural biotechnology cluster [20]. In business case study A, AAFC Sainte-Foy, Université Laval, and Medicago would be considered a part of the Québec City life sciences cluster (see Figure 4.3). This cluster consists of biopharmaceuticals, bio-diagnostic tools, medical equipment manufacturing, nutraceuticals, and telemedicine [105]. Medicago reduced the transaction costs and therefore increased its probability of commercial success (as discussed in the beginning of this section) by building on background knowledge from informal inter-institutional relationships in the research cluster (AAFC, Université Laval, etc.) Our findings are further supported by an economic analysis of the Saskatoon agricultural biotechnology cluster [20].

Table 4.3: Research Phase: Institutional Structure Analysis (From [20]).

| Institution | Characteristics |
|----------------------------------|---|
| Optimal Institutions | <ul style="list-style-type: none">• Long term contract or hierarchical relationship |
| Actual Institutions | <ul style="list-style-type: none">• Short-term, one-time contracts involving multiple partners operating with incompatible and/or competitive operating mandates creates pressures to negotiate all benefits in a single process |
| Institutional Options | <ul style="list-style-type: none">• Long-term renewable contracts with more chances for rebalancing benefits and costs over the longer term• Embedding of the negotiations and contracts in networks or clans, such as the agricultural biotechnology cluster in Saskatoon |

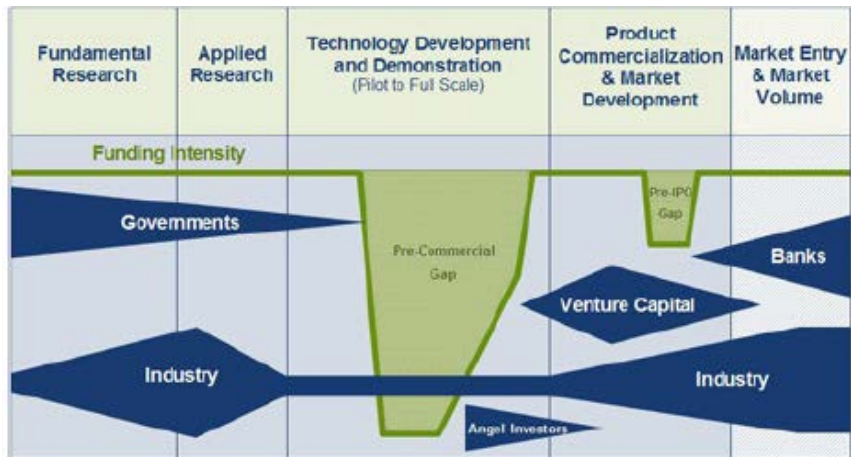


Figure 4.2: Financing Gaps as an Entry Barrier (Death Valley) for Introduction of New Technologies (From: [http://www.sdte.ca/index.php?page=about-our-funds&hl=en_CA]).



Figure 4.3: Location of Québec City Life Sciences Cluster [Google Maps Canada; <http://maps.google.ca/> Retrieved on 20 May 2010].

Legend: The locations are circled in red; AAFC and Canadian Red Cross Society are located in Sainte-Foy.

To better understand how clans reduce the transaction costs, one has to consider regional systems of innovation or industrial clusters operating as hybrid actors in Figure 1.4 (the intersecting areas labelled B, D, F, and G, the domain of networked knowledge). In the Saskatoon cluster, informal inter-institutional relationships between public research institutions, a public university, and private companies enables learning from their collaborations, thereby adding further to the know-how knowledge and providing a visible, efficient point of entry for know-how and know-who. These clans are not always restricted to geographical proximity as illustrated in business case study B by partnership of Dow AgroSciences, Biodesign Institute at ASU, Washington University, Boyce Thompson Institute for Plant Research, and Benchmark Biolabs, Inc.

4.3.2 Gestation Phase

This phase involves taking the results of the research activities from the research phase and determining how to optimize their commercial and social benefits [20]. This includes the following: (a) proof of concept (for definition, see Appendix A); (b) newly generated knowledge/IP protected with appropriate mechanisms, i.e., patents, copyrights, trademarks, trade secrets, plant breeders' rights released into the public domain in the form of publications and public repositories deposit; and (c) gaining some results of research that need approval from appropriate regulatory authorities for further use. The relationships between influencing factors and their implications on strategic goals are outlined in Table 4.4.

Table 4.4: Implications of Goals and Technical Factors in the Gestation Phase (From [20]).

| Factor | Implications |
|--------------------------|---|
| Strategic Goal | <ul style="list-style-type: none">• Protection of intellectual property resulting from the research phase• Achieving regulatory approval and market introduction |
| Technical Factors | <ul style="list-style-type: none">• Low-frequency transactions involving high-task programmability, low non-separability and high asset-specificity |

Costs involved in the gestation phase are highly significant. They are represented by the negative amplitude in Figure 3.7. Costs involved in proof of concept can vary and run into millions of dollars [20]. In terms of knowledge exchange, proof of concept likely involves the know-how of the research team to develop the methodologies and to undertake the experiments required to demonstrate the efficacy and scientific merit of the invention. This could simply be viewed as an obvious extension of the research phase [20]. In vaccine research, proof of concept involves successful completion of all four phases of clinical trials in human volunteers, where efficacy and safety of the candidate has been established (Figures 1.1 and 4.1). Data from 2007 indicate that the cost of patenting process, including initial drafting of the application through prosecution of the patent application, allowance, issuance, and post-issuance maintenance of the patent, can easily run from US\$30,000 to US\$50,000 in legal and patent-office fees [106]. The cost of regulatory compliance ranges from US\$1.5 million for simple plant transformations, to US\$75 million for a new therapeutic pharmaceutical (where only one in ten succeeds); and initial public offerings (IPO) generally cost a minimum of 10% of any market offering (2005 figures) [20]. In 2006, Medicago raised gross proceeds of \$2,003,834 by IPOs on the TSX Venture Exchange

[81]. This figure above is helpful in making a comparison between the amount of money raised by Medicago IPO and the cost of patenting/regulatory compliance.

Using the theoretical framework outlined in Chapter 3, the thesis identifies the types of knowledge generated and used, and the institutions needed to handle the transactions and relationships. The optimal, actual, and potential institutional structure(s) to handle the exchange of the factors that influence generation and use of knowledge are outlined in Table 4.5.

Table 4.5: The Gestation Phase: Optimal, Actual, and Potential Institutions (From [20]).

| Institution | Characteristics |
|------------------------------|--|
| Optimal Institutions | <ul style="list-style-type: none"> • Joint ventures |
| Actual Institutions | <ul style="list-style-type: none"> • Each partner institution owns IP discovered by their researchers and is responsible for commercializing this property • IP is highly fragmented, and often inaccessible, due to lack of access to tacit knowledge |
| Institutional Options | <ul style="list-style-type: none"> • New joint venture, either between projects and research networks, or with a commercial agent (e.g., VIDO-Pyxis Genomics) |

In order to better understand the deals and knowledge exchanges involved, a discussion of the paper trail leading to one of the significant exchanges in business case study A is described. In September 2008, PMI announced they offered to acquire 49.8 per cent of Medicago for an

investment of \$15,975,000 [107] and acquisition of one seat on Medicago's Board of Directors [70]. The paper trail is outlined below.

In February 2007, Medicago made a contact with R&D executives from PMI at BioPartnering North America meeting in Vancouver. PMI have a good understanding of the genomics of tobacco, and had plans to diversify its portfolio and do something beneficial with the plant other than manufacture cigarettes. PMI had sent its executives to look for "adjacent technologies" for the tobacco plant [70]. Medicago was looking for financing to initiate human clinical development of their lead H5N1 influenza vaccine in 2009. At the Vancouver meeting, Medicago was successful in convincing PMI to invest in Medicago's research project with their value proposition (higher speed, and cost-effective, highly scalable pandemic vaccine production). In October 2008, PMI subsidiary Phillip Morris Products (PMP) and Medicago entered into a joint pandemic and seasonal influenza research program. The terms of the agreement stipulated that Medicago will hold rights to arising IP from the program, and PMP will be granted a licence on such arising IP.

Two weeks after the Vancouver meeting, PMI visited Medicago to verify the science, vet management's credentials, and check that the facilities could handle a scale-up of production. In December 2007, PMI contracted Medicago to manufacture a specific (confidential/unknown) molecule [70]. Satisfied with the delivered results, in January 2008, PMI acquired Medicago's licensed pandemic and seasonal influenza vaccine production in tobacco platform technology.

In September 2008, with its \$15,975,000 investment, PMI got 49.8% stake and a board seat at Medicago. For Medicago, the deal provided PMI's scientists and many resources to be available for the research project [70]. In December 2009, Medicago reported positive results from Phase I clinical trials [108], which indicated the first step in proof of concept.

Transactional Forms: These transactions are relatively low-frequency with high task-programmability, low non-separability (the ability to succeed in any single step in the gestation period is fundamentally affected by the contributions of the entire team); and high asset-specificity (approval at any stage is specific to the product or technology). These technical factors are outlined in Table 4.5.

Institutional Structures: Mahoney [41] describes joint ventures as the optimal institutional form, with shared investments and shared equity in the results of gestation phase. Our findings from business case study A further confirm Mahoney's framework, as reported above (section 4.3.2). In this case, PMI forms a joint venture with Medicago for an influenza vaccine development program, with \$15,975,000 investment (shared investment) for 49.8% equity (shared equity). In this structure, Medicago owns rights to arising IP from the joint program and PMP (PMI) is automatically granted a licence on such arising IP.

4.3.3 Adoption Phase

As the companies we studied in our business case studies have not passed the gestation phase, further discussion presented would be entirely of conjecture with practical consequences.

Continuing the discussion, ideally, proof of concept would have been achieved, by the end of gestation phase. IP protection of invention would have been granted, a working prototype of the product(s) developed, and required regulatory approvals granted. The adoption phase involves marketing the results of the research, i.e., achieving optimal adoption of the technology or product and realizing a return on that activity.

Transactional Forms and Institutional Structures: Technology adoption could take several pathways. First, if the research project managers develop and produce their technology or product directly, that would involve search, negotiation and enforcement costs; if, on the other hand, the technology were to be sold or licensed to others, then the main cost would be related to enforcement [20].

The theoretical framework outlined in Chapter 3 suggests IP for sale and licenses would be best handled in the context of longer-term relationships (e.g., joint venture, long-term contract, or hierarchy). Almost any organizational option (e.g., from short/long term contracts, clans, strategic partnerships, to joint ventures, etc.) could work for direct production and sale.

Findings in this thesis indicate that the second pathway seems to be what Medicago is taking. Between July 2009 and March 2010, Medicago had negotiated and/or signed three commercialization agreements with three corporate entities in five different regions. These

regions were France, India, the Middle East and North Africa, and Japan. The objective for using a Medicago technology platform to complement existing domestic influenza vaccine production infrastructure in these regions was to offer surge capacity of influenza vaccines before the first wave of a pandemic.

Conditional to Medicago delivering certain results (e.g., phase I clinical trials), it was anticipated that some of these above-mentioned corporate entities (licensees) would get non-exclusive licenses to manufacture pandemic and seasonal influenza vaccine by territory (regions), and Medicago would in turn be able to receive revenue streams for specified sales and/or units manufactured. Medicago's short term corporate strategy of building on their strengths in drug development for proof of concept, and then forming partnerships in manufacturing and marketing further substantiates the projections made in this thesis. Completion of these license deals would require a great amount of due diligence in terms of licensee compliance and IP enforcement.

Here again value of partnership as an enabling mechanism is being highlighted. By negotiating partnership agreements with entities that have established manufacturing facilities and marketing networks to license out its platform technology, Medicago built on its strength of drug development. By doing so, it potentially shortened the time to manufacture vaccines and reach a larger and wider market. Previous research to this thesis has identified potential advantages of partnership in manufacturing as faster than building in-house, and in marketing, potentially opening new channels to reach existing customers, and creating access to new customers [68].

4.3.4 Knowledge Stock Phase

The continued benefits of the generated knowledge, also known as knowledge stock phase, provide a basis for future research. This knowledge stock phenomenon is considered a social benefit of research and implicitly acknowledged in the “public good” agenda at most universities and public research institutions, but has not been incorporated into their IP management plans in any strategic way [20].

As the “patent and then publish” drive is gaining momentum at public research institutions [20], advantages of knowledge stock have been severely diluted. This is because once the knowledge generated is protected by patent, the knowledge is never considered to be released in the public domain, even though much of it holds no current or future commercial value. Many universities and public research institutions have a stated preference and a policy to license their IP widely rather than to a single entity in order to get maximum public good. It is observed that this creates a hold-up problem, as most new technologies require further investment to develop lack financial commitment (a pull force), as private investors realize that competition (wider-scale licensing) reduces their ability to recoup their expenses for further development [20].

Institutional Structures

Mahoney [41] suggests clans or clusters would be optimally suited to manage knowledge in this phase. It is also suggested that hybrid institutional structures (B, D, F, and G in Figure 1.4) in the realm of networked knowledge would pool IP that would be licensed or cross licensed with ongoing research communities [20].

4.4 Conclusion

An analysis of two separate business case studies attempting to commercialize PDVs has been presented. Situated within the theoretical framework of transaction forms and institutional structures, this section offered a detailed analysis of the types of knowledge generated and used, and the institutions required to handle the transactions and relationships in each phase of development. Thesis findings indicate that the dominant institutional structure during the research phase is clans (research cluster). It is indicated that transaction costs have been reduced by building on background knowledge from informal inter-institutional relationships in localized research clusters. Analysis of the gestation phase indicates joint venture is the dominant institutional structure, with shared investment and equity. The literature and thesis projections suggest SMEs partner with companies that have established manufacturing facilities and marketing networks in the adoption phase. The literature suggests clusters would be optimal institutions in the knowledge stock phase.

5. CONCLUSIONS AND FUTURE WORK

5.1 Introduction

Vaccines are considered to be one of the most successful and cost effective weapons against infectious diseases to date [3]. Traditionally, vaccines have been produced to provide protective immunity prior to exposure to infection causing microorganism (prophylactic vaccines), but vaccines (or immunotherapeutics) that can stimulate immunity in an already infected individual are also gaining importance [4].

Vaccines can be classified based on their constitution: killed, intact virus; live, weakened virus; killed, intact bacteria; live, attenuated (or weakened) viruses; a mixture of inactivated toxins; killed, “disrupted” viruses; and a mixture of highly purified complex sugars taken from bacterial coats or capsules. Newer approaches that have been adopted include subunit and recombinant vaccines. Gene-based and virus-like particles (VLPs) are new vaccine technologies in the R&D stages. Novel adjuvants and delivery systems are also being developed to complement the emerging vaccine technologies.

Vaccines have made a comeback from being considered low-profit, high-risk biological products to high-profile stars due to a multitude of factors including multibillion dollar sales, pandemic influenza demand, and increased public and private investment in vaccines.

Currently, licensed vaccines produced in mammalian cell lines, yeast, and the common enteric bacterium *E. coli* have their associated technical problems, including scalability, contamination, and complex modifications. A decade-old R&D project of developing vaccines in plants has yielded promising results addressing the above-mentioned issues to a great extent with the added benefit of faster and cheaper production; these are proposed to play an important role in complementing conventional vaccine supply [12].

The 2009–2010 influenza pandemic presents an opportunity to capitalize on the strengths of PDVs. Considering competitive advantages in terms of higher speed and lower cost that are of great importance in pandemics, PDVs are clearly positioned to complement, if not substitute, conventional pandemic (and seasonal) influenza vaccine supply.

5.1.1 Public Good Vs. Private Interests

Public, market, and voluntary sectors have already been reviewed in section 3.2 (and Figure 1.4). The public sector pursues policies to maximize the interests of society altogether. It is optimally suited to create public-good, know-why scientific knowledge and uses a social welfare evaluation framework for decision making. The market sector owns property and attempts to maximize profits on those investments. It uses valuation models derived from accountancy to optimize the net present value of investments in technology development [20].

According to Phillips and Dierker [109], since the 1980s, the government policies aimed at accelerating private research and commercialization have resulted in private ownership in agricultural biotechnology, which has created certain challenges and a shifting of benefits to

private entities. These challenges include the slowing down of basic research generation, restricted freedom to operate at the development stage, and negative impact on consumer acceptance (and therefore commercialization) due to a shortage of independent verifiable research on health, safety, and economic impacts of new agricultural biotechnology products.

Public good and private interests in vaccine innovation can be best understood from the critical analysis of push and pull force mechanisms. Relation of push and pull mechanisms to innovation process has been discussed in section 2.2.

5.2 Research Work Done

A broad approach to research has been undertaken in this thesis focusing on an interdisciplinary approach to analyzing PDV innovation. Sections of this thesis have been dedicated to presenting the potential benefits of PDVs in terms of cost efficiency and timeline of production while maintaining quality and sterility. This presentation ultimately forms the basis of exploring PDVs as an option in achieving self sufficiency of vaccine production against infectious diseases in developing and underdeveloped countries. The institutions responsible for vaccine innovation, introduction, and regulation in Canada have been mapped. A detailed analysis of the regulatory environment for biotechnology products with secondary input from general food and drug regulation has been undertaken and documented. This analysis and discussion serves as an important resource for academic, government, and industry discourse on potential regulatory framework for PDVs. An analysis of social issues surrounding vaccines and GM crops with implications for PDVs has been presented. A study on current and emerging frameworks for improving access to vaccines in LMI countries has also been presented.

Socio-economic frameworks of knowledge generation and use, and organizational forms have been used to critically analyze PDV innovation in Canada. Networked knowledge is of particular interest in this thesis, and the ways companies do transactions in research and product development networks have been presented. Also, it was found that (i) new research-intensive biotechnology SMEs can reduce their transaction costs by working in research networks (primarily PPP), and (ii) by forming strategic partnerships with companies that have established manufacturing and distribution networks, these SMEs increased their chances of accessing capital and other resources. This significantly increases probability of commercial success by SMEs in a highly competitive environment of the global vaccine business.

5.3 Policy Implications

Policy implication findings from this research project for the public sector and private industry are documented below.

5.3.1 Public Sector

The immense public good importance of vaccines has already been established earlier in this chapter (section 5.1.1). Governments worldwide should recognize this importance and include plans for introducing new and improved vaccines into their national procurements. PDVs are well positioned to take the lead in this respect, especially in the developing and underdeveloped countries, because of faster and cheaper production. In addition, governments worldwide, including those of developed countries, should recognize, facilitate, and streamline introduction of PDVs to complement pandemic vaccine supply for shorter production times, safety, and socio-economic advantages. It was concluded in a 2008 publication that the remaining scientific

and technological challenges being surmountable, the successful strategy for PDVs has to rely on continued public support as an investment in public good [12].

An interesting model of vaccine development is PREVENT. As discussed in section 2.2 (Control Priorities and Health Capacity Pull), PREVENT is a public vaccine initiative that will act as a catalyst by conducting pre-clinical and clinical trials to make vaccine candidates attractive for receptor manufacturing companies by shouldering the risk of early-stage vaccine development. PREVENT has significant public investment in terms of funding from Networks of Centre of Excellence—Centres of Excellence for Commercialization and Research, usage of publicly funded research facilities at VIDO, and leveraging the expertise of publicly funded scientists and researchers. PREVENT will continue to benefit commercially and scientifically should it build on background knowledge from informal institutional relationships in the research network. Building on background knowledge from informal institutional relationships in the research network was shown in subsection 4.3.1 (Transaction Forms and Institutional Structures > Characteristics) to reduce transaction costs. As PREVENT derives its strength in pre-clinical and clinical research, it is important in the early stages to identify and build relationship with potential companies who would be interested in moving the vaccine candidate from clinical stage to manufacture and distribution. PREVENT is significant to both local and national economies, as it employs scientists and researchers locally, and provides potential vaccine manufacture and sales nationally.

Public sector support for PDVs is discussed in the paragraphs below. With the Pharma-Planta Project (2.2 subsection Technology Push), initially started by the EU, public funding as a technology push for PDVs is coming to fruition in the form of spinoffs and product development collaborations with the industry, as documented below.

The Fraunhofer-Gesellschaft and its wholly owned subsidiary Fraunhofer USA, Inc. are non-profit R&D and contract research organizations. Fraunhofer USA, Inc. with its headquarters in Plymouth, Michigan, presently is composed of seven research and development units, and the Fraunhofer Centers, including the Fraunhofer Center for Manufacturing Innovation (CMI) and the Fraunhofer Center for Molecular Biotechnology (CMB). CMB, CMI, the Boston University College of Engineering, and the biopharmaceutical company iBio, Inc. in Newark, Delaware have developed a fully automated, scalable, natural (non-GM) green plant technology platform that, according to news release, efficiently produces large quantities of vaccines and therapeutics within weeks of disease outbreaks [115]. A three-year research collaboration between CMB, CMI, and the Boston University resulted in this unique PDV technology platform with scalable automated processes, and it further established the first cGMP (current Good Manufacturing Practices) pilot manufacturing facility located in Newark, Delaware. The design and construction of the pilot facility was facilitated by public funding in the form of support from the Defense Advanced Research Projects Agency (DARPA), the US Department of Defense under the Accelerated Manufacturing of Pharmaceuticals program, along with funding from the State of Delaware. This technology platform (iBioLaunch™) uses plant viral vector technology developed by CMB and robotic automation designed by CMI, and its IP/technology is owned by iBio (a PPP model). On 20 September 2010, an IND application filed by iBio, Inc. with the US

FDA for a vaccine candidate was accepted. It is anticipated iBio, Inc.'s rapid vaccine production facility will play a crucial role in addressing and containing future pandemics and emerging biological threats. iBio, Inc. is also party to an agreement supporting access to medicines in developing and underdeveloped countries. According to the agreement, CMB will use iBio's technology under a non-exclusive, non-royalty-bearing grant to develop and test new Global Health Vaccines funded by the Bill & Melinda Gates Foundation (research and product development funds push, see section 2.2, subsection Research and Product Development Funds Push) [94].

G-Con, LLC and the Texas A&M University System have designed Project GreenVax in Bryan, Texas to show proof of concept initially to produce candidate H1N1 vaccines [116]. The idea is to produce the vaccine in a large-scale production facility with a projected final scale capacity of 100 million doses per month using tobacco plants grown hydroponically in a contained environment. Majority of funding for the project is public funding provided by DARPA.

It has been well documented (see the two DARPA funded projects above) and argued [16] that the apparent acceptance by the relevant funding agencies in the USA of rapid response vaccines easily produced in plants and aimed at potential bio-terror and pandemic agents such as influenza, anthrax, and haemorrhagic fever viruses is a positive step in the right direction. It is also argued that niche market of "orphan disease" and low-margin vaccines such as for Lassa fever, the South American haemorrhagic fever viruses, meningitis vaccine (see Meningitis Vaccine Project in 2.3), and other low-volume markets would be obvious first targets, other than the military options if acceptance does happen soon [16]. Increasing acceptability in the long

term could mean a shift to the mainstream high volume/low cost generics market, which potentially can be realized by PDV technology in ensuring access to medicines in the undeveloped and developing countries.

5.3.2 Private Companies

The industry as a driver of vaccine innovation in terms of R&D, manufacturing, and distribution is well recognized, and has been covered in section 5.1. The industry is anticipated to actively participate in the vaccine innovation, playing an equal role in social responsibility, environmental stewardship, and positive economic activity, along with the public and voluntary sectors.

It is argued that it will take the incremental successes of plant-made therapeutics (such as essential metabolic enzymes and monoclonal antibodies), followed by vaccines for livestock/companion animals and human therapeutics such as insulin and vaccines (e.g., Icon Genetics/Bayer Innovation's patient-specific vaccines for the treatment of non-Hodgkin's lymphoma) to finally tip the balance for broad-based acceptability of PDVs for human use [16]. The thesis shows new research-intensive biotechnology SMEs can reduce transaction costs by forming PPPs in research networks, and can gain access to capital and other resources by forming strategic partnership with other companies that have established manufacturing and distribution networks. These factors are attributed to increased probability of the SME to succeed commercially in highly competitive environment of global vaccine business.

5.4 Challenges and Limitations

As no PDV product has reached the market yet, events under study are still under development.

Based on this limiting factor, the final story might look different.

5.5 Extensions

So far, this analysis has focused on biotechnology business case studies in North American PDV innovation. An extension of this research program would be to study PDV innovation worldwide. This would include approaches for rapid, streamlined, and sustained introduction and adoption of PDVs against infectious diseases in developing and underdeveloped countries where they are most urgently required. Regulatory systems differ by geographic regions, countries (e.g., Europe, Asia, and South America), and social dynamics. Studying the potential introduction and adoption of PDVs is important because of its role as a LMI country oriented public health tool.

5.5.1 Future Work

Further work needs to be done to analyze institutional structures in developing and underdeveloped countries where the vaccines would be manufactured and distributed. This work would streamline and facilitate the humanitarian adoption of PDVs to these regions.

Interdisciplinary study is strongly needed to better understand the principles and implications of international trade agreements and access to vaccines to facilitate the adoption of PDVs.

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